PROCEEDINGS
OF THE
ROYAL SOCIETY OF MEDICINE
Vol. 49 No. 9 September 1956

CONTENTS

Continued overleaf

CONTENTS (*continued*)

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Section of Neurology

President—REDVERS IRONSIDE, F.R.C.P.

[*January* 5, 1956]

DISCUSSION ON THE CLINICAL CONSEQUENCES OF CEREBRAL ANOXIA

Dr. R. S. Allison (Belfast):

The industrial aspects of anoxia have lost much of their former significance owing to improved conditions and ventilation in factories and workshops. Unfortunately the same cannot be said of domestic and accidental coal-gas poisoning which causes some 500 deaths annually in England and Wales (Thelwall Jones, 1955) and is one of the chief sources of anoxic admissions to hospital. Hypoxic effects are seen too with comparative frequency in medical practice, and, as these do not always receive the recognition that is their due, I propose to refer briefly to them first.

HYPOXIC EFFECTS IN MEDICAL PRACTICE

They arise as side effects of injury, disease or as a consequence of medical or surgical treatment. Cerebral circulatory failure, dehydration, the incautious use of barbiturates or other potentially histotoxic drugs, and disturbances in electrolyte balance are the most common exciting causes.

Under normal metabolic conditions the brain is the most susceptible of organs to reduction in its oxygen supply. Not only must oxygen be available, but the cerebral blood flow must be adequate; it is not surprising therefore in medical practice that cerebral circulatory failure should be one of the chief causes of hypoxic effects. Two ways in which these may be brought about are: (1) By failure of the pumping action of the heart, (2) by diminution in the total blood volume, whereby the work of the heart (however efficient it may be) is rendered ineffectual. Typical examples of the first kind are cardiac arrest and chronic congestive heart failure. Patients in chronic congestive failure become irritable, drowsy, confused and disorientated because their cerebral blood flow is slowed and cerebral oxygen consumption significantly reduced (Scheinberg, 1950). Exsanguination from post-partum or gastro-intestinal hæmorrhage is an instance of the second kind.

Dehydration and electrolyte imbalance.—The examples so far given are fairly concrete; anoxic symptoms are so pronounced and the cause so patent that there is little difficulty in their recognition. But for each classical example of anoxia seen in practice there must be five or more other cases in which the mechanism is not so clear, or in which more than one factor causing anoxia is at work. Thus, toxic-confusional reactions are often seen in patients whose fluid intake is inadequate; where there is vomiting or diarrhœa, or where fluid is being lost in some other way, so that, unless it is replaced, dehydration and disturbance in electrolyte balance result. It is not so long ago since the cerebral symptoms of dehydration were attributed to increased permeability of the blood-cerebrospinal fluid barrier permitting toxins from the alimentary tract to reach the brain, but it is now known that dehydration exerts its effects by causing diminution in cerebral blood flow and creating stagnant hypoxic conditions. Mishaps of this kind are liable to occur especially in elderly arterio-sclerotic persons, e.g. after operations for cataract, and illustrative cases have been described elsewhere (Allison, 1952).

Chronic duodenal ulcer is another source of such cases. Here, in addition to dehydration the noxious effect of alkalosis may be added, as was first noted in this country by Cooke (1932). Alkalosis is especially liable to occur in cases where there is renal damage, pyloric obstruction or excessive use of alkalis. Although probably less potent in its effects than dehydration, alkalosis induces cerebral hypoxia by high blood pH levels interfering with dissociation of oxyhæmoglobin. It is not often one has either the opportunity or means of confirming this statement but, through the courtesy of Professor G. M. Bull, I have learned of a case which I have his permission to mention.

Case I.—A man of 39 who had been in the habit of taking alkaline stomach powder five times daily for some years on account of dyspepsia associated with chronic duodenal ulceration. Although there was no radiological evidence of obstruction, he had been vomiting, and on admission to hospital was in a drowsy, confused mental state, resisting examination. The results of investigations of the blood are as follows (normal values in brackets) : Packed cell vol. 32·5% (48%), plasma vol. 1·33 l. (3 l.), total blood vol. 1·97 l. (6 l.), blood urea 622 mg.% (20–40 mg.%), chlorides 450 mg.% (365 mg.%), Na 309 mg.% (330 mg.%) CO_2 comb. power 100 vol.% (55–70 vol.%), blood pH 8·0 (7·25), Effective renal flow 15 ml./min., glomerular filtration rate 5 ml./min., urine flow 2·5 ml./min. Samples of blood were taken from the internal jugular vein and oxygen saturation was found to be 33 and 38% in two samples. Allowing for the pH of the blood at the time, and reading from

Barcroft's curves for oxyhæmoglobin dissociation at different pHs, oxygen saturation in the cerebral tissues must have been about 8–10 mm.Hg in comparison with the normal figure of 35 mm.Hg.

Hypoxic symptoms often mistaken for hysteria.—There is another point relating to the symptoms displayed by these patients. In sick persons the symptoms of hypoxia are less sharply defined than they are in healthy subjects. When a healthy person is exposed to hypoxia his sudden unaccountable muscular asthenia, aggressiveness, absentmindedness or senseless repetition of actions at once draw attention to him. Textbooks stress these points but, in persons already sick and confined to bed, such premonitory symptoms as headache and blurring of vision may pass unnoticed and disturbances of behaviour, due to the clouding of consciousness, may readily be mistaken for hysteria. It is important in such cases always to look for signs of perseveration which is a reliable guide to the presence of organic clouding of consciousness, and usually pathognomonic of it. A simple test is to ask the patient to put out his tongue and then, when he has done so, to close his eyes. Perseveration may also be apparent when a patient, having repeated the days of the week correctly, and being asked to name the months of the year, goes on repeating the days. Another useful guide to the presence of organic clouding of consciousness is inability to reverse simple series, e.g. counting from 1 to 20 and then counting backwards from 20 to 1. A third reliable indicator is the presence of disorientation, loss of temporal and spatial orientation being usually indicative of deeper clouding of consciousness than the presence of temporal disorientation alone.

Clinical Effects of Severe Anoxia

These minor hypoxic effects, which I have emphasized purposely, are usually recoverable and due to reversible changes in cellular function; the same applies to many cases of coal-gas poisoning. In the majority of these full consciousness is regained within a few hours, recovery is uneventful and there are no sequelæ. The plantar reflexes at first are often extensor in type, but they quickly revert to normal, the sign when present alone having no particular significance.

Prognosis as to survival.—When anoxic exposure is severe death usually results without the patient regaining consciousness. It follows that when the duration of anoxia is unknown, and the patient still unconscious when first seen, it is extremely difficult to estimate the prospects of survival. Dilatation of the pupils, the recurrence of repeated epileptiform fits and sweating are ominous features, but otherwise one cannot judge by the clinical signs alone. Thus one patient, a woman aged 60 and the victim of accidental coal-gas poisoning, was unresponsive to painful stimuli, breathing stertorously and displaying conjugate deviation of the eyeballs. Her limbs were rigid, the arms flexed at the elbows and wrists, the legs extended and the plantars doubly extensor. Yet she recovered full consciousness within eight hours, whereas another patient suffering from coal-gas poisoning whose condition was very similar, a young man aged 25, remained in coma and died on the third day. The difference lay not so much in the clinical signs they presented as in the relative severity of their exposures to anoxia.

Survival after severe anoxia is rare and purchased as a rule at the cost of irreversible and widespread damage to the nervous system. My own personal experience of such instances, over a period of several years, amounts only to 15 cases. In all of these cases initial recovery of consciousness was slow, coma or drowsy stupor persisting for twelve to forty-eight hours and full consciousness not being regained for several weeks or months. Survival is improbable when coma persists for twenty-four to forty-eight hours but de Ajuriaguerra and de la Vigne (1946) have reported recovery in several cases after coma had lasted from 48 to 70 hours. As regards the validity of claims for compensation in industrial accidents, Hunter (1955) states that, to be considered reasonable, there should be, not only clear evidence of anoxia, but continuous unconsciousness for at least six hours after return to the fresh air.

Before considering the neurological sequelæ of anoxia there are two other aspects of prognosis which require mention. First, *unexpected recovery after severe anoxia* is extremely rare but authentic instances are on record. For example, Kossmann (1947) reported the case of an airman whose oxygen failed at 25,000 feet for a period of ten minutes, and there is Turner's (1950) case of a young man whose heart stopped beating for seven minutes. Three minutes of cardiac arrest usually results in irreversible damage to the brain (Lucas, 1953), but in this case, although for a year or more the patient showed signs of impaired cerebration, after two years he had recovered and there were no traces of his former disabilities.

Also remarkable was the case of a woman of 70 seen in 1947 who showed no permanent ill-effects after severe coal-gas poisoning (Allison, 1950). Unaware of a leak in the main gas pipe, she and her husband (also aged 70) retired to bed one night and were not discovered until forty-eight hours later, when neighbours broke in and found the couple still in bed, the man dead and the woman in deep coma. For the first two days she lay in semi-coma but by the third day showed signs of recovering consciousness, when it was apparent she

had a right-sided hemiplegia. By the seventh day she was wakeful, able to sit up and the hemiplegia was improving. She could make small talk but was totally disorientated in time and space and confabulating freely. Her mood was one of fatuous euphoria and in this state she remained for eighty-eight days. By then, however, all traces of residual hemiplegia had disappeared and she had regained orientation, memory for past events and insight. There was no sign of subsequent deterioration, and she was seen at frequent intervals throughout the next two years. Unfortunately when she died later of bronchopneumonia, no post-mortem examination was carried out.

Second, *temporary survival* in a comatose or vegetative state is also uncommon. Thus, a case fully reported by Pineas (1924) lingered for seven weeks whereas Howkins, McLaughlin and Daniel's (1946) case died on the twenty-sixth day. Until recently I had not seen such a case survive for longer than a few days. However, I have had one recently where the survival period was nearly six months.

Case II.—A child aged 7, whose heart stopped beating for ten minutes on October 13, 1955, death not occurring until April 2, 1956.

For the first three days after the anoxic experience she remained in deep coma; on the fourth day weak withdrawal responses were elicited to painful stimuli. Recurring tonic convulsive seizures were then seen between the third and tenth day, in which the head became retracted, limbs extended, trunk arched, wrists and fingers strongly flexed and feet plantar-flexed. After these fits had ceased spontaneously, about the tenth day the child was observed to show some change of facial expression when her mother spoke to her insistently, and it was evident she could hear although she was blind. A few days later, before the end of October, respiration was accompanied by phonation and the limbs were beginning to show signs of increasing spasticity. From that time there was no further improvement. About a month after the onset she developed torsion dystonia (Fig. 1) and involuntary trombone tremor-like movements of the tongue (Fig. 2). These recurred frequently whenever she was disturbed and continued at the rate of 2–4 per second for several minutes at a time, chewing movements of the lower jaw occurring simultaneously. However, they ceased spontaneously after three to four weeks and, like the fits, did not subsequently recur.

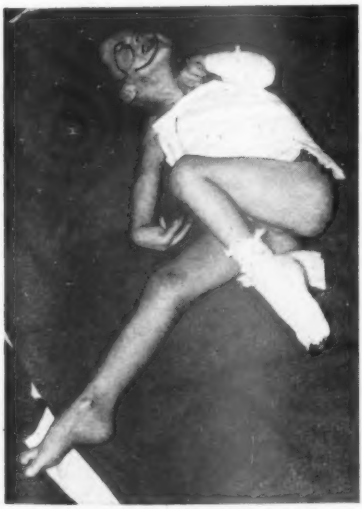


FIG. 1.—Cerebral anoxia in a child aged 7. Photograph taken one month later, illustrating posture of torsion dystonia.

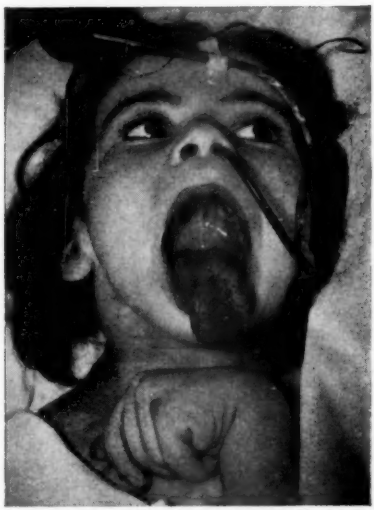


FIG. 2.—Cerebral anoxia in a child aged 7. Illustrating curious protrusion of tongue, which was the site of rhythmical involuntary movements.

Although this little girl was seriously and permanently disabled, incapable of utterance other than crying and phonation, and blind, there was evidence (apart from circumstantial observations at the bedside) that she was capable at times, of some cerebral activity and that her hearing was relatively intact. A completely flat record was obtained on electroencephalography. Haglund (1952) obtained a similar result in an anoxic decerebrate infant. In my patient the featureless character of the record could not be altered by causing her to breathe pure oxygen or mixtures of oxygen and carbon dioxide. Stroboscopic stimulation had also no effect. However, the effect of slowly injecting Pentothal Sodium intravenously

was to set up some slow wave activity at frequencies of 2–3 c/s. That some hearing was retained and that she was capable of attending to certain stimuli was shown when a favourite toy—a musical box—was placed beside her and played; at once her breathing became faster and frequent blinking movements of the eyelids were observed.

Neurological Sequelæ in Survivors After Severe Anoxia

The principal features seen in the 15 cases with neurological sequelæ are as follows:

S. M'C., male, aged 47. 6.8.52. Electrocution. Retrograde amnesia of some minutes, post-anoxic amnesia three days. Chronic amnestric syndrome with expressive dysphasia and reading disability, constructional apraxia.

B. M'C., male, aged 60. 29.5.50. Respiratory arrest at operation; comatose for twelve hours. L. hemiplegia (after some days). Jargon aphasia at first; later persistent nominal defects and agraphia with visual object agnosia and constructional apraxia. Chronic amnestic syndrome.

J. M'D., male, aged 41. 13.6.52. Two minutes' cardiac arrest during surgical operation for mitral stenosis (valvulotomy). Coma followed by incoherent talk, muttering delirium. No dysphasia but grossly disorientated. Cortical blindness. R-L disorientation and finger agnosia. Death after some months.

D. M., male, aged 19. 20.7.55. Cardiac arrest during surgical operation. R. hemiparesis and sensory impairment with half visual field defect; later objects recognized on previously blind side but visual inattention persisted. R-L disorientation, dyscalculia, occasional finger agnosia. Constructional apraxia. Improving.

R. M., male, aged 70. 7.2.50. Accidental coal-gas poisoning. Retrograde amnesia of some hours, post-anoxic amnesia 1 week. Transient finger agnosia and R-L disorientation with constructional apraxia but recovered fully.

A. B., male, aged 56. 19.1.53. Cardiac arrest during surgical operation. Status epilepticus with myoclonic jerking. Decerebrate posture. Death on fourth day.

A. N., male, aged 7. 21.6.53. Respiratory difficulties during an abdominal operation. Status epilepticus. Decerebrate rigidity. Death on tenth day.

F. C., female, aged 22. 26.7.55. Valvulotomy. Cortical blindness, disorientation, perseveration. Partial recovery of vision but persistent defects chiefly in R. half field.

G. C., male, aged 22. 19.6.46. Coal-gas poisoning. Remained in semi-coma. Death on third day.

L. R., female, aged 70. 25.11.47. Accidental coal-gas poisoning. Prolonged post-anoxic psychosis. R. hemiplegia. Constructional apraxia. Ultimate recovery.

L. M., female, aged 6. 13.10.55. Cardiac arrest during abdominal operation. Survived for six months. Status epilepticus, involuntary tongue movements, postural dystonia, blindness.

W. M., male, aged 24. 28.11.43. Anoxic as result of an explosion on board ship. Prolonged post-anoxic psychosis followed recovery from coma. Later signs of Parkinsonism and chronic amnestic syndrome supervened.

M. B., male, aged 47. 16.5.42. Anoxic as result of an explosion on board ship. Prolonged post-anoxic psychosis. Later showed constructional apraxia and developed chronic amnestic syndrome.

F. H., male, aged 31. 16.5.42. Anoxic as result of an explosion on board ship. Post-anoxic psychosis with amnesia of several weeks' duration. Later developed chronic amnestic syndrome with paraphasia and constructional apraxia.

O. B., male, aged 47. 16.5.42. Anoxic as result of an explosion on board ship. Post-anoxic amnesia one week. Developed a chronic amnestic syndrome with constructional apraxia and signs of Parkinsonism.

Epilepsy was seen in 3 patients; in 2 the development of status epilepticus heralding death, and in the third (the case described earlier), a residual state of partial decerebration. In one of these cases of status epilepticus, a man aged 56 (A. B.), not only did fits recur until death, but in the intervals between them there was myoclonic jerking of the limbs, face and jaws. These were most pronounced and occurred spontaneously although they could be elicited by tapping over muscle, by stimulation with a flashing light or a sudden loud noise. They could not be evoked by pin-prick, to which the depth of unconsciousness had apparently rendered the patient insensitive.

Three of the patients developed *hemiplegia* but ultimately recovered full function of their limbs. Hemiplegia, when it occurs as a sequel of anoxia, is usually not apparent for some days, and reaches its maximum between the seventh and fourteenth days. In one case (D. M.), it was accompanied by gross sensory impairment and neglect of the ipsilateral arm, but I have not seen any cases with gross disturbances of body image as have been described by Solomon (1932).

In 2 cases *Parkinsonism* was observed. Like hemiplegia, its development takes place insidiously some weeks or months after anoxia. In one of de Morsier and Georgi's (1940) cases symptoms were apparently not noticeable until a year had elapsed. In my cases the symptoms were mild in their extent: coarse tremor of the tongue of trombone type, plastic increase of tone in the limbs, facial immobility, and in one case there was typical pill-rolling tremor. Both cases were followed up, and in one (W. M.), the signs were no longer apparent two years after the anoxic event. Nielsen (1943) has reported similar recovery after three

years. Incidentally, another anoxic patient, not included in this series, was already suffering from post-encephalitic Parkinsonism when, in a fit of despondency, he attempted to gas himself; although several hours unconscious, he recovered and displayed no evidence of worsening in his neurological status. Yakowley (1944) described old cystic areas of softening distributed symmetrically in the pallidum of a man surviving forty-nine years after gas poisoning. Grinker's (1926) fully detailed case only survived two months.

Passing to the incidence of residual defects in intellectual function, these may be considered first as regards symptoms which could be attributed to general "knocking off" of cerebration, changes in mood and behaviour, impairment of memory for past events and disorientation. All of the survivors showed defects of this kind. As regards more specialized defects, residual disturbances of *speech* after consciousness had been regained, were seen in 4 cases. One patient (B. M'C.), showed a babble of talk amounting to jargon aphasia for some weeks but more often anoxic survivors are silent and bereft of spontaneous speech, or if they speak do so hesitatingly, leaving sentences unfinished. Many of them have difficulty in naming objects and perseveration is partly responsible for this difficulty; they are better at naming sighted objects than doing so from memory and make little use of gesture and periphrasis. In one case (F. H.), there was a marked paraphasia four months after he had been rendered anoxic. He was euphoric, but partly aware of his speech difficulty for he admitted that when he could not remember a name he did his best to improvise. There was impairment of articulation, and this (with his paraphasia) rendered speech almost unintelligible at times. At other times he was fairly good and could name common objects correctly. But when shown a picture of a tent he described it first as "a camp", then as "a hut" . . . 'trench" . . . "tent" A picture of a bear he described as "a tiger" . . . "leopard" . . . "beast".

Blindness was a sequel in 4 cases. In one of these, L. M., the child with postural dystonia, there was marked papilloedema and retinal congestion. In 3 other cases blindness was of cortical type, although one found it most difficult to be sure about this (B. M'C., J. M'D., F. C.). However, by comparison with the case reports of others (Adler, 1944; Wechsler, 1933) they appeared to fall within this group. Thus in one case (F. C.), a young woman with mitral stenosis, whose symptoms followed an operation for valvulotomy, consciousness was regained on the first day, but on the next she complained of inability to see and became greatly distressed. Those in charge of her case were inclined to think her hysterical as, indeed, seemed likely at the time. Cerebral embolism was considered unlikely as no clot had been found in the auricle at operation, there was no calcification and the heart sounds were regular. However, the pupils were semi-dilated and reacted only sluggishly to light. She could tell when light was flashed in her eyes but was unable to recognize any objects. There was marked perseveration in action and speech and she was totally disorientated in time. Vision recovered within a week sufficiently to enable her to recognize objects, but she is left with permanent field defects chiefly in the left half field.

In the other cases in which repeated observations were made the pupillary responses to light varied from day to day, usually being present and sluggish, but occasionally absent. As in the foregoing case there were no disc changes. The existence of blindness was not recognized by either of them and the symptom was associated with temporal and spatial disorientation, a mood of facile euphoria, difficulty in repeating days of the week backwards, defective registration and recall of fresh data. Anosognosia was pronounced and in one case (J. M'D.), there was, in addition, right-left bodily disorientation, and inability to count or to name the fingers. Despite these defects this patient showed no speech disturbance and had no difficulty in recognizing the nature of objects by touch or in some instances, by hearing. He displayed no ideomotor apraxia.

Performance from day to day in these patients with cortical blindness varies considerably. One day they may recognize some objects and not others, another day fail entirely to recognize anything. Disturbances of figure-background relationships can often be demonstrated by holding up an object and asking the patient to identify it; he may peer intently in the general direction, his hand stretching out exploringly and taking another object, e.g. a handkerchief protruding from the examiner's coat pocket. Similarly, in cases where cortical blindness is transient and recoverable, a stage may be reached when an object is identified without difficulty against a plain background but not against an assortment of other objects. Affective influences also appear to play some part in determining which objects are recognized.

All anoxic patients were tested for signs of *Gerstmann's syndrome* but this was found only on three occasions. Finger agnosia and right-left disorientation are believed to represent disorders of body imagery, but it has been suggested that right-left disorientation may be due to semantic errors on the part of the patient, arising out of associated speech disturbance. However, in all three instances in which the syndrome was present, general spatial and temporal disorientation co-existed, and when this was regained right-left disorientation and finger agnosia disappeared. This suggests that the two are related, right-left disorientation being a fragment of total disorientation and not the result of semantic errors. Further, one

has the impression that during recovery of consciousness patients first became aware of their bodies and later of their environment, and this may account for the comparative infrequency of the syndrome at a time when there is still gross general spatial disorientation.

By contrast, *constructional apraxia* is seen with greater frequency in post-anoxic cases. Ideomotor apraxia is well recognized and several instances of it have been reported in the literature, but it is more a symptom of the earlier stages of recovery of consciousness. Constructional apraxia may persist (almost as an isolated residual defect) for some weeks or months after full consciousness has been regained. This is an important point for, if allowed to return to work, such patients get into immediate difficulties through their inability to undertake any formative or creative tasks, whether these involve the assembly of complicated apparatus or simply laying the table for tea. Sticks or match tests (after Goldstein), Kohs' blocks or drawing tests have been used as simple clinical tests for uncovering the defect and have proved most valuable.

The fact that constructional apraxia is encountered so often in post-anoxic states, and that it tends to disappear in time, leads one to think that, like Gerstmann's syndrome, it cannot be related solely to a focal lesion in one part of the brain, but that it depends for its existence on widespread disturbance of function in both hemispheres. Indeed the clinical consequences of anoxia afford unrivalled opportunity for investigation in this field. The biochemical lesion may affect some parts of the brain more than others, but it probably does so more or less diffusely and symmetrically. Consequently, in recoverable cases (and these form the majority) one can observe the different phases through which cerebral functioning must pass between total dissolution and final reintegration, By doing so it is possible further insight may be gained into the mode of production of such symptoms in patients with purely focal cerebral lesions.

REFERENCES

ADLER, A. (1944) *Arch. Neurol. Psychiat., Chicago*, **51**, 243.
AJURIAGUERRA, J. DE, and VIGNE, A. R. DE LA (1946) *Sem. Hôp. Paris*, **22**, 1950.
ALLISON, R. S. (1950) *Schweiz. Arch. Neurol. Psychiat.*, **66**, 1; (1952) *Brit. med. J.*, ii, 1286.
COOKE, A. M. (1932) *Quart. J. Med.*, **1**, 527.
GRINKER, R. (1926) *J. nerv. ment. Dis.*, **64**, 18.
HAGLUND, G. (1952) *Acta chir. scand.*, **102**, 364.
HOWKINS, J., MCLAUGHLIN, C. P., and DANIEL, P. (1946) *Lancet*, i, 488.
HUNTER, D. (1955) The Diseases of Occupations. London.
JONES, T. A. (1955) *Brit. med. J.*, ii, 373.
KOSSMANN, C. E. (1947) *J. Aviat. Med.*, **18**, 405.
LUCAS, B. G. B. (1953) *Irish J. med. Sci.*, No. 331, 280.
MORSIER, G. DE, and GEORGI, F. (1940) *Rev. med. Suisse rom.*, **60**, 1038.
NIELSEN, J. M. (1943) *Bull. Los Angeles neurol. Soc.*, **8**, 22.
PINEAS, H. (1924) *Z. ges. Neurol. Psychiat.*, **99**, 36.
SCHEINBERG, P. (1950) *Amer. J. Med.*, **8**, 148.
SOLOMON. A. P. (1932) *Med. Clin. N. Amer.*, **15**, 531.
TURNER, H. (1950) *J. Neurol. Psychiat.*, **13**, 153.
WECHSLER, I. S. (1933) *Arch. Ophthal., Chicago*, **9**, 957.
YAKOWLEY, P. I. (1944) *Arch. Neurol. Psychiat., Chicago*, **51**, 494.

Dr. P. D. Bedford (Oxford):

Transitory mental confusion is almost a normal concomitant of illness in old people (Bedford, 1954). It is usually a non-specific manifestation, of no localizing value, of disease or disturbance often quite remote from the brain. There are four main reasons for the brain in old age being so sensitive an "indicator" of disordered function anywhere in the body:

(1) The brain at any age is extremely vulnerable to anoxia (Courville, 1939; Hoff *et al.*, 1945; Corday *et al.*, 1953) because of its complete dependence on the aerobic production of energy from glucose (Himwich, 1951). The relative immunity to anoxia of the brain of the newborn which might be expected theoretically owing to the short-lived persistence of anaerobic glycolysis as a source of energy (Himwich, 1951) is not clinically apparent (Read, 1955).

(2) The brain is probably more sensitive to lack of oxygen than any other organ or tissue of the body. Not all parts of the brain are equally sensitive, however; consciousness is lost within 45 sec. in complete oxygen-deprivation; the cortical neurones in the supra-granular laminæ cannot survive more than 4 min. of anoxia; and 10 min. is probably the outside limit for survival of any of the nerve elements of the brain (Hoff *et al.*, 1945).

(3) The supply of oxygen to the brain is dependent upon the state of the heart, the lungs, the blood and the blood vessels; the composition of the respiratory gases; and the integrity of such homœostatic mechanisms as the sino-aortic and spinal baroceptor reflexes. Cerebral cellular metabolism derives its energy from oxygen and glucose but also depends upon a supply correct in amount and proportion of ions including Na, K, Ca, H, and phosphorus, and substances including water, amino acids, fats, glucose, enzymes and co-enzymes: these

in turn are dependent upon the state of the liver and kidneys. the endocrine glands (for such substances as insulin and thyroid hormone), the intestines and the composition of the diet.

(4) The cerebral circulation tends to become impaired in old age (Himwich, 1951) and derangement of function of other organs occurs more readily because of their lowered "reserve".

It is, therefore, not surprising that the brain in old age is a sensitive "indicator" of disordered function anywhere in the body, and that geriatric practice provides a fruitful field for a study of the clinical effects of cerebral anoxia. These reasons also explain why the effects of cerebral anoxia are usually non-specific in the sense that the same clinical pattern may be produced by widely different ætiological factors.

It may be useful here to recapitulate briefly some physiological principles relating to cerebral anoxia—by which is meant a condition of oxygen lack in the brain from any cause.

Four types of anoxia are still generally recognized: (1) Anoxic—when the oxygen tension in the blood is lower than normal. (2) Anæmic—when the amount of functioning hæmoglobin is reduced but the arterial oxygen tension is normal. (3) Stagnant—in which the blood supply to the tissues is insufficient but the arterial oxygen tension is normal. (4) Histotoxic—when the cells are unable to utilize effectively the oxygen supplied to them.

(This classification is arbitrary and incomplete. For example it takes no account of the essentially anoxic effect of hypoglycæmia or disturbances in the potassium-sodium-calcium ratio: these, however, can be "forced" into the "histotoxic" group.)

Certain types of anoxia are potentially more dangerous than others, the deciding factor being the availability of oxygen to and within the cells. For example, in anoxic anoxia due to the respired atmosphere being poor in oxygen, the lowered oxygen tension in the blood stimulates breathing and results in CO_2 being "washed out" of the blood. Thus, not only is there too little oxygen in the blood, but the oxygen which is present is less readily available to the tissues because the concomitant reduction in CO_2 tension impedes the dissociation of oxyhæmoglobin—the curve is "shifted to the left". In these circumstances, any increased demand by the cells for oxygen may further aggravate the anoxia.

Again, the anæmic anoxia of carbon monoxide poisoning is much more serious than a hæmorrhagic or Addisonian anæmia in which the amount of functioning hæmoglobin is reduced to the same degree; for carboxy-hæmoglobin impairs the dissociation of oxyhæmoglobin and so the oxygen which *is* present is less readily available to the cells. Similarly the histotoxic anoxia due, for example, to narcotic drugs or cyanide is potentially very serious for the cells are rendered unable to utilize the oxygen supplied to them. There is a parallel between this type of anoxia and the effect on the brain of hypoglycæmia in which the cells are unable to utilize oxygen by being deprived of the energy mechanism for doing so.

There are, as has been indicated above, very many conditions which may produce cerebral anoxia (Bedford, 1955) including cerebral circulatory failure from any cause (Corday *et al.*, 1953) and general and cerebral metabolic disturbances (Allison, 1952). In clinical practice, it is often not possible to determine with accuracy the immediate cause of damage, for multiple factors and more than one type of anoxia frequently coexist in the same patient.

Examples of some factors which should be constantly borne in mind are as follows:

(1) The routine (and therefore indiscriminate) prescription of such drugs as morphine, atropine, hyoscine and barbiturates as pre-operative and post-operative medication to patients young and old, and without knowledge of the individual's sensitivity to them.

(2) Pyrexia and toxic-infective states (e.g. cystopyelonephritis following prostatectomy) render the brain more susceptible to anoxia by increasing its basal oxygen consumption (Himwich, 1951). This may well be a factor in the development of the dementia seen occasionally after prostatectomy (Bedford, 1955).

(3) The sino-aortic and spinal baroceptor reflexes which normally maintain cerebral blood flow may be abrogated in general and spinal anæsthesia and in the hypotension deliberately induced with the methonium and allied compounds to facilitate surgery. Blood supply to the brain may thereby be imperilled and risk of cerebral anoxia enhanced by such otherwise innocuous manœuvres as movement of the patient or alteration in his posture.

I shall not attempt a comprehensive survey of the clinical effects of cerebral anoxia. Some are adequately dealt with in the standard textbooks of physiology, aviation medicine, pædiatrics, anæsthesia, &c.; others, e.g. cough syncope, have recently been intensively reinvestigated; some have been described by Dr. Allison. The effects of sudden, subacute and chronic anoxia in healthy adults are well known—due in great measure to heroic experiments performed on themselves by physiologists and naval and air-force volunteers. (It is perhaps surprising that the Air Forces of this country and the U.S.A. have no record of examples of permanent damage to the brain in survivors of aviation anoxic episodes (Campbell, 1955; Kilpatrick, 1955).)

I shall limit my discussion to some interesting clinical effects of cerebral anoxia which I feel have received less attention than they merit. They fall into two broad groups, namely:

A. Transient or apparently fully reversible effects.

B. Permanent cerebral incapacity of varying degree.

Although experimentally it may be possible to produce cerebral ischæmia independently of anoxia—each showing characteristic histological changes (Hoff *et al.*, 1945)—it is very difficult to envisage cerebral ischæmia occurring clinically without cerebral anoxia. I shall therefore assume throughout that the essential effect of cerebral ischæmia is anoxia and shall not attempt a clinical separation.

A. *Transient or Apparently Fully Reversible States.* (The reservation is made because I have not attempted detailed psychometric testing before and after the event.)

In most of these states the patient is aware, on recovery of full consciousness, that he has been mentally confused—and often in what way. Some of them appear to be of the nature of unduly prolonged, exaggerated and vivid dream-states.

(1) *Sleep-disturbances.*—These take the form of disturbed and restless sleep, nightmares unduly and unusually vivid dreams, and occasionally somnambulism, in patients who have previously not been so disturbed. They occur in patients with heart failure, emphysema and lung failure, and in toxic and febrile conditions.

Case I.—H. L., a man aged 72, had for three weeks suffered from terrifying dreams; he would awaken in the night, panic-stricken, screaming and breathless. His dreams were of different content, but were always vivid, well remembered and terrifying. He had never previously been similarly afflicted. He complained of dyspnœa on effort for the same period but had no cardiac pain. He was in left ventricular failure due to a cardiac infarction. He made a good recovery. A precisely similar series of symptoms occurred sixteen months later. He died suddenly of a coronary thrombosis nearly two years after the first episode. Necropsy showed no notable cerebral abnormality.

(2) *Hypnagogic confusion.*—This occurs quite commonly in healthy people at any age but rarely lasts more than a few minutes. In old people, however, a state of disordered consciousness with loss of contact with reality and mental confusion may last for as long as two hours after half-awakening from sleep and may cause alarm and worry to the patient and to his relations. This state occurs in toxic and febrile conditions, in old people suffering from the effects of cerebral arteriosclerosis and particularly following sleep induced with barbiturates and other potent hypnotic drugs. It probably reflects an undue depression of the respiratory centre during sleep.

The confusion has sometimes been aborted by lobeline or nikethamide given intravenously, when "control" injections of "normal saline" and inhalation of oxygen have failed.

(3) *Iatrogenic confusional states.*—Although such conditions can be permanent and occasionally catastrophic, they are very rarely so (these will be discussed later). But a transient state of mental confusion induced by drugs is extremely common, is often unrecognized and is very frequently treated with the very drugs which produce it!

Case II.—H. B., a man aged 68, was given morphine to alleviate low back pain believed to be due to a vertebral metastasis from prostatic carcinoma. He became a little strange in his manner but still complained of pain and was therefore given more morphine. His mentality rapidly deteriorated; he became aggressive, noisy, difficult to control and doubly incontinent. Over the next twelve hours, morphine, hyoscine and repeated doses of a mixture of chloral hydrate, potassium bromide and opium produced no improvement. He did not recover his normal mental state until twenty-four hours after admission to hospital. He died of uræmia seven weeks later. Necropsy showed no notable cerebral abnormality.

Although the results of bromide intoxication are widely known, far too little attention is paid to the anoxic and histotoxic effects of potent narcotic and analgesic drugs. They readily produce mental confusion in old people and do much to exacerbate any coexisting mental impairment. They should be used with caution and discrimination in old people, and, where sedatives are specifically indicated, drugs such as paraldehyde, chloral or methylpentynol should be tried first.

(4) *Nocturnal confusional states.*—In these there is often delirium, increased motor activity, violent or disordered behaviour and sometimes hallucinosis. Characteristically the patient is mentally quite normal during the day and remembers his mental confusion of the previous night. The disordered behaviour can be so disturbing as to lead to the patient's committal to a mental hospital. When due to lowered cardiac output in heart failure (stagnant anoxia) it frequently responds dramatically to aminophylline given intravenously, but very rarely to oxygen for the arterial oxygen tension is normal. When due to the anoxic anoxia of lung disease immediate treatment is disappointing, but oxygen and lobeline are occasionally helpful. This type of confusion is also seen in toxic, infective, and pyrexial conditions and in uræmia and pyelonephritis.

(5) *Periodic breathing.*—This is a physiological phenomenon during sleep in infancy and is sometimes observed in apparently healthy old people during deep natural sleep. It is seen not infrequently in patients with heart failure, uræmia and chronic anæmias, cerebral arteriopathic conditions, during sleep induced by narcotic drugs and in respiratory and

cerebral disease. It is thought to be due to depression of the respiratory centre and is sometimes associated with lesions of the brain stem. It may be accompanied by fluctuating consciousness and vasomotor disturbances. It usually responds to aminophylline either intravenously or in suppositories. When due to anoxic anoxia and if aminophylline fails, it may respond to oxygen and intravenous lobelline or nikethamide.

(6) *Some other reversible organic cerebral reactions.*—This miscellaneous group is characterized by an apparently completely reversible cerebral reaction including mental confusion, deterioration in personality, intellect and habits, &c., of longer duration than those described above but lasting little longer than the precipitating cause is operative.

Case III.—A. K., a married woman aged 78, suffers from idiopathic aplastic anæmia and has been kept alive for two and a half years by blood transfusions. Whenever her hæmoglobin level falls below 50% (Haldane) she becomes mentally confused, agitated, hallucinated, deluded, incontinent of urine and fæces, and difficult to manage. She is invariably restored to mental normality by blood transfusion. (This case is an example of the effects of cerebral anæmic anoxia.)

Case IV.—E. O., an unmarried woman aged 59, has for many years been crippled with rheumatoid arthritis. She was admitted to hospital with persecutory delusions, incontinence of urine and fæces, noisy, confused and difficult to manage. She was found to be thyrotoxic. Her mental state recovered completely after five weeks of treatment with antithyroid drugs. Two relapses were precipitated by withdrawing treatment and were relieved each time by reinstituting it. Her cerebral condition appeared to be directly related to the degree of thyrotoxicosis as measured by the B.M.R. and radioactive iodine tracer tests. (This appears to be an example of cerebral anoxia due to excessive demand for oxygen by the cells.)

Similar cases occur due to anoxic anoxia in acute bronchitis, bronchopneumonia and other respiratory disorders; and due to both anoxia and histotoxic anoxia, not infrequently, in patients poisoned with hyoscine, barbiturates and other potent hypnotic and analgesic drugs. It is well known, too, that similar transitory confusional states often occur in elderly people following operations under general anæsthesia.

The rapidity with which the organic cerebral reaction due to "cerebral circulatory failure" precipitated by such conditions as acute left ventricular failure, and the hypotensive ("shock") states of coronary thrombosis, acute hæmorrhage and pneumonia can sometimes be reversed is often remarkable: full mental equilibrium has been restored on occasions with the needle still *in situ* during the course of an intravenous injection of aminophylline, a blood transfusion or an infusion of nor-adrenaline. (The rare occurrence of permanent cerebral incapacity associated with these same conditions is discussed later.)

(7) "*Organic neurasthenia*" is a much misused diagnosis which has consequently fallen into disrepute. As defined by Lewis (1947), however, it remains a useful title for a syndrome whose chief features are irritability, languor, fatigue, emotional hypersensitiveness, irascibility, mood disorders, headache, impairment of memory and difficulty in concentration. It occurs as a result of many physical causes, including such anoxic episodes as acute hæmorrhage, operations under general anæsthesia, asphyxia during dental and out-patient nitrous-oxide administration, anoxic pulmonary heart failure, and overdosage with morphine, hyoscine and barbiturates. It tends to recover slowly but completely after the precipitating factor has ceased to operate (Lewis, 1947), but may occasionally be permanent.

(8) *Transient focal neurological signs* (e.g. a rapidly recovering hemiplegia) have been observed in association with conditions causing "cerebral circulatory failure" and are due presumably to "stagnant" anoxia since necropsy has failed to reveal focal cerebral damage. The association of such rapidly reversible cerebral states with the shock of cardiac infarction is well attested (Bean and Read, 1942; Cole and Sugarman, 1952; *Lancet*, 1952). These focal signs are difficult to explain. Possibly there is a coincidental minor cerebral vascular abnormality which escapes detection; the turbulence effect of such an abnormality could well give rise to a pressure drop between the main and subsidiary streams. There are many possible explanations but none which has been proved or which is entirely satisfying.

B. *Permanent Cerebral Incapacity.* The principal groups to be discussed here are the major and minor dementias. In a previous paper (Bedford, 1955) I have reported the occurrence of extreme dementia in 18 previously mentally normal old people following operations under general anæsthesia, while 91 suffered lesser degrees of intellectual impairment. But major and minor degrees of cerebral incapacity following anoxic episodes are by no means limited to old people, nor to operations under general anæsthesia.

(1) "*Organic neurasthenia.*"—Although full recovery is the rule (as has been indicated above) this may be a permanent consequence of cerebral anoxia. The clinical picture merges imperceptibly with that of the lesser degrees of dementia which form the next group. I have no doubt that intellectual deterioration is common to both groups, but in the absence of detailed psychometric testing before and after the event, I have separated them here.

Case V.—H. B. S., a man aged 63, is a retired company director. Four years ago he developed bronchopneumonia and was gravely ill for three weeks, two of which were spent in an oxygen tent, his life despaired of. He made a full physical recovery but since then has been irritable and easily fatigued; he is given to outbursts of irrational anger and weeps uncontrollably at even trivial upsets. He retired three years ago because of his inability to concentrate and has shown no improvement despite faithful adherence to medical advice.

(2) *Minor dementias.*—These comprise minor degrees of impairment of memory, intellect and performance, deterioration in the personality and habits, and lessened emotional control. This clinical picture has been observed following operations under general anæsthesia, dental and out-patient "gas", severe acute hæmorrhage, pneumonia, and overdosage with barbiturates, hyoscine and morphine.

Case VI.—Mrs R. W. N., aged 33, was a vivacious woman, a good conversationalist, and a competition bridge-player. Besides being a competent housewife and the mother of two children, she acted as secretary to her husband—a busy dental surgeon. Five years ago a fingernail was avulsed in the out-patient theatre under general anæsthesia (thiopentone followed by nitrous oxide and oxygen). Recovery was delayed and she was detained in hospital for thirty-six hours. Since then she has been dull and has lost her vivacity. She is forgetful and cannot play bridge. She is faulty at adding up simple sums of money when shopping and is unable to help her husband with his work. She herself says "I don't know what's wrong, but it seems that my mind is foggy—like the 'before taking' picture in the advertisements".

These minor dementias, like the "organic neurasthenias" cause great distress, not only to the patient, but also to his relatives and friends, the tenor of whose complaints is remarkably uniform: "He's just not the same person since . . ." "He's never read a book through since . . ." "She's lost all interest in the family since . . ." "He's never been able to write a decent letter since . . ."

In those of higher intellectual status these minor dementias are even more distressful, and they may be incapacitating to one whose interests and work demand protracted mental effort and concentration; thus the difficulty experienced by a history don in concentrating over a book, and the impairment of memory sustained by a practising surgeon after undergoing prostatectomy, proved so disabling that neither was able to continue his vocation.

The situation is not improved by the misdiagnosis of such cases as "hysteria" and "neurosis" in the young (as was Case VI; and *vide* Cartwright, 1955), and "senility" in the old.

(3) *Extreme dementia.*—This comprises a state in which the deterioration in intellect is so gross that the individual is virtually a human vegetable—unable to help himself, wet and dirty, and mentally inaccessible. Recognizable syndromes within this group include the "decorticate" and "decerebrate" states similar to those following severe head injury. Between this group and the minor dementias there are cases which show intermediate degrees of severity; rarely the Korsakoff syndrome is seen. The clinical patterns are, however, non-specific in the sense that the same picture can be produced by any of the many causes of cerebral anoxia.

I shall attempt only a very simple classification by separating the complex "operation under general anæsthesia" group of cases from those in which a single factor appears to be chiefly operative. Only one case-history will be given in detail for they are all essentially the same in that the patients were mentally quite normal before the episode but abjectly demented following it.

(i) *Extreme dementia following operation under general anæsthesia.*—Of 29 such cases, 18 were operated on while under my supervision so that I was able to compare their mental state before and after operation (Bedford, 1955).

Case VII.—M. S., a woman aged 82, was an intelligent, kindly person—a voracious reader and fond of an argument. She did excellent needlework and was a friendly and helpful neighbour.

While walking in the street she tripped over the kerb and fractured the neck of her right femur. On admission she gave an excellent account of herself. Her hip was pinned under general anæsthesia.

On recovery she was noisy, confused, irrational, incontinent of urine and fæces and mentally inaccessible. She was given sedatives and analgesic drugs with no improvement, but thereafter she slept for long periods. There were no post-operative chest complications; her blood urea, ECG, and blood pressure were normal; there were no abnormal neurological signs. She remained in a state of extreme dementia until her death, three months later, from bronchopneumonia and bedsores. She was doubly incontinent, unaware of her surroundings, and unable to recognize her former intimates.

(ii) *Cerebral circulatory failure* (Corday *et al.*, 1953).—(*a*) *Hæmorrhage:* 5 cases of gross dementia following massive acute hæmorrhage from the intestinal or genito-urinary tract have been recorded (Bedford: to be published).

(*b*) *Hypotensive* ("*shock*") *states:* (i) Cardiac infarction (4 cases); and (ii) pneumonia (4 cases), have precipitated extreme dementia (Bedford: to be published); (iii) severe diarrhœa:

Case VIII.—S. P., a man aged 80, suffered permanent extreme dementia following severe hypotension (B.P. 60/?) lasting for two hours and due to diarrhœa caused by acute salmonella dysentery.

(c) *Cardiac arrest:* (i) During surgical operations on patients young and old.

(ii) In a Stokes-Adams attack:

Case IX.—E. E., a woman aged 78, had for six months suffered infrequent Stokes-Adams attacks due to complete heart block. A period of cardiac asystole lasting six minutes was observed and recorded electrocardiographically. She subsequently recovered consciousness and survived for seventy-two hours in a "decorticate" state.

(iii) *Carbon monoxide poisoning* and *status asthmaticus* need no further mention.

(4) *Localized cerebral damage.*—Transient focal neurological signs associated with the shock of cardiac infarction have already been mentioned. Permanent focal cerebral damage is a well known occasional sequel to anoxic episodes—e.g. Parkinsonism following carbon-monoxide poisoning.

An interesting association which appears to have received little attention in the literature is the occurrence of focal cerebral infarcts in cases of anoxic pulmonary heart disease (cor pulmonale). I have observed 4 such cases (Bedford: to be published):

Case X.—G. C., a man aged 42, had epileptiform convulsions on two occasions during the eighteen months he survived following the diagnosis of congestive heart failure due to chronic bronchitis with emphysema. An executive dysphasia was followed fifteen months later by a left hemiparesis, and both persisted until he died. He had been in sinus cardiac rhythm throughout, and his cerebral vessels were natural at necropsy, yet he had one large infarct in the right hemisphere and several smaller ones in both.

Conclusion.—Although the majority of my examples are drawn from geriatric practice, it must not be assumed that cerebral anoxia is withstood with impunity by younger people. The apparent relative immunity of the young is probably due to their greater "mental reserve" (for they have not yet developed the cerebral circulatory impairment of senescence) and hence to the greater rapidity with which they compensate for any damage they suffer.

A most interesting and puzzling question which emerges from a study of the clinical effects of cerebral anoxia is why they occur so uncommonly. Although very many patients are exposed to serious degrees of anoxia, yet dementia following these episodes is comparatively rare. In an attempt to explain this I have assumed an individual idiosyncrasy—a personal susceptibility—to anoxia in those who suffer cerebral damage. But whether this idiosyncrasy to anoxia is a property of the brain itself, or of the baroceptor reflex mechanisms as has been suggested to me by Dr. Bourne (1955), or of something as yet not defined, I am quite unable to form an opinion. Whatever the cause, however, the risk must be constantly borne in mind. Asphyxia masquerading as anæsthesia; "hypotensive surgery"; the routine (and hence indiscriminate) use of potent hypnotic and analgesic drugs pre-operatively and post-operatively, and in the management of elderly confused patients, are all unjustified. Cerebral anoxia demands immediate relief by urgent removal of the responsible cause.

REFERENCES

ALLISON, R. S. (1952) *Brit. med. J.*, ii, 1286.
BEAN, W. B., and READ, C. T. (1942) *Amer. Heart J.*, **23**, 362.
BEDFORD, P. D. (1954) *Oxf. med. Sch. Gaz.*, **6**, 9; (1955) *Lancet*, ii, 259.
BOURNE, J. G. (1955) Personal communication.
CAMPBELL, P. A. (1955) Personal communication.
CARTWRIGHT, F. F. (1955) *Lancet*, ii, 392.
COLE, S. L., and SUGARMAN, J. N. (1952) *Amer. J. med. Sci.*, **223**, 35.
CORDAY, E., *et al.* (1953) *Arch. Neurol. Psychiat., Chicago*, **69**, 551.
COURVILLE, C. B. (1939) Untoward Effects of Nitrous Oxide Anæsthesia. Mountain View, Calif.
HIMWICH, H. E. (1951) Brain Metabolism and Cerebral Disorders. Baltimore.
HOFF, E. C., GRENELL, R. G., and FULTON, J. F. (1945) *Medicine, Baltimore*, **24**, 161.
KILPATRICK, J. (1955) Personal communication.
Lancet (1952) i, 653.
LEWIS, A. (1947) In: Price's Textbook of the Practice of Medicine. 7th Edit. London; p. 1856.
READ, G. D. (1955) Personal communication.

Professor A. Meyer (London): *Neuropathological Aspects of Anoxia*

The investigation of anoxia has been one of the major contributions made by neuropathology during the last decades. It would be quite impossible to give an adequate review on this occasion of the numerous important papers which have been published on the subject. In these circumstances, it seems appropriate to confine myself to one type of anoxia for more detailed description and to utilize my experience of other types of anoxia as a background for the discussion of some relevant problems. I have chosen the anoxia due to anæsthesia since there has been, to my knowledge, only one full pathological report of a relevant case in this country (Howkins *et al.*, 1946). Moreover, the subject has gained importance through Bedford's (1955) publication on the effect of anæsthesia in the elderly.

My own experience in death following anæsthesia has been in both human and experimental pathology. The experimental investigations were published with Blume in 1934. The 6 human cases have not yet been published although some have been demonstrated jointly with Dr. Turner McLardy.

TABLE I.—SUMMARY OF FINDINGS IN 6 HUMAN CASES OF DEATH FROM ANÆSTHESIA

Number	Age and sex	Anæsthetic	Arrest	Survival	Cortex	White matter	Striate body	Pallidum	Ammon's horn	Cerebellar cortex	Other subcortical centres
I	54, F.	Ether	Cardiac (15–20 min.)	3 days	+++	−	+++	+−	+++	+++	Thalamus ++
II	46, M.	Ether	Respir, and cardiac (A few min.)	4 days	++	+ −	−	−	++	+++	
III	42, M.	N_2O	Respir. (A few min.)	56 hr.	+++	−	+++	+++	+++	+++	Subst. nigra reticulata ++
IV	38, F.	N_2O	Cardiac and respir. (A few min.)	44 hr.	+++	−	+	+	+++	+++	Thalamus ++
V	53, M.	N_2O + Ether	Cardiac (25 min.)	36 hr.	+++	−	+++	+++	++	+++	Thalamus +++ Corpus luysi + Dentate nucleus ++
VI	38, F.	N_2O (Avertin)	Cardiac (1 min.)	6½ mth	+++	+++	+ −	+++	+++	++	Thalamus ++ (retrograde degeneration) Dentate nucleus + Amygdaloid nucleus +

Table I gives the main clinical and pathological data of the human cases. There were no major differences between nitrous oxide or ether cases. All cases had cardiac or respiratory arrest or both. There was neither clinically nor at necropsy any conspicuous anomaly which might have been implicated for the respiratory or cardiac complication. The duration of arrest, as far as it is known, ranged from one minute (Case VI) to twenty-five minutes (Case V). While the lesions in Case V were the severest in this series, they are not much less severe in Case VI. In 5 cases the survival was short; Case VI survived six-and-a-half months, in a condition of severe dementia.

On histological examination, severe lesions were seen in all cases in the cerebral cortex, cornu ammonis and cerebellar cortex, while the cerebral white matter was affected in only one case. The striate body and globus pallidus were damaged in most cases, often jointly. The thalamus was severely affected in 3 cases, ignoring the probably retrograde degeneration in Case VI. The reticular zone of the substantia nigra, the corpus luysii and the dentate nucleus were each involved only once. No definite changes were seen in hypothalamus, red nucleus, compact zone of the substantia nigra, geniculate bodies, and the inferior olives. There was, however, in the last case, evidence of an amygdaloid lesion.

I must confine myself to this rather summary description; it is hoped that a full publication of some of these cases will be carried out in due course jointly with my collaborators.

It is interesting to compare these human cases with experimental data in 30 cats (anæsthetized by ether or by ether+CO_2) of which 5 showed irreversible histological changes (Table II). All 5 of these cats had respiratory or cardiac arrest of at least five minutes. All other animals in which no such complete arrest had been effected, showed no significant histological changes. It is of particular interest that the brain of one cat which had suffered a cardiac arrest of as long as ten minutes was histologically normal.

The lesions were similar to those reported in the human cases. The thalamus was not recorded as damaged but the absence in the list of this centre and of other subcortical centres may be due to the lack of attention on our part to these areas; the slide material is unfortunately no longer available for fuller study.

TABLE II.—SUMMARY OF FINDINGS IN 5 CATS SUBMITTED TO ANÆSTHESIA (MEYER AND BLUME, 1934)

Cats	Anæsthetic	Arrest	Survival	Cortex	White matter	Striate body	Pallidum	Ammon's horn	Cerebellar cortex	Other subcortical centres
1	Ether	Respir. and cardiac (10 min.)	4 days	+++	−	++	++	+++	++	Subst. nigra reticulata+
2	Ether	Respir. (10 min.)	6 days	++	+	++	−	+	++	
3	Ether	Respir. and cardiac (5 min.)	6 days	++	+	−	+++	+	−	
4	Ether and CO_2	Respir. (10 min.)	8 days	−	−	−	+	+	−	
5	Ether and CO_2	Respir. (18 min.)	3 days	−	++	+++	++	++	++	

DISCUSSION

In all human and experimental cases with irreversible pathological lesions, cardiac or respiratory failure had invariably occurred. The experimental series is particularly informative, as it shows that none of the animals without respiratory or cardiac stoppage showed any appreciable histological change. In Bedford's recently published cases, no complete arrest seems to have occurred although considerable hypotension was described in at least two. However, none of our cases belonged to the category of the elderly; it might well be that in the elderly lesser disturbances of the circulation and respiration may suffice to produce irreversible lesions resulting in dementia. Unfortunately, in none of Bedford's cases is the histology given because of the difficulty of distinguishing between post-anoxic and senile vascular lesions. Although this may be true in some cases, I believe that it is often possible to identify anoxic lesions by the combination of cortical or—alternatively—white matter lesions with cerebellar and basal ganglia lesions. In view of the practical and theoretical importance of this material it would be most valuable if, in spite of the difficulties, all cases of the elderly suspected of death from anæsthesia, should be submitted to full neurohistological investigation.

The lesions in almost all human and experimental cases were severe and widely distributed. They would indeed account for the dementias which have been described after anæsthesia and other types of anoxia including irreversible hypoglycæmic coma and carbon monoxide poisoning. The dementias produced in this way may be so profound as to give rise to an erroneous diagnosis of protracted coma or hysterical pseudodementia. On the other hand, cases with strictly localized brain damage do occur; in a fully investigated case of carbon monoxide poisoning, unilateral softening of the globus pallidus was the only lesion we found. Likewise, bilateral softening of the reticular zone of the substantia nigra was in one dog the only appreciable histological effect of experimental cyanide poisoning (Meyer, 1933).

In general, the localization of the lesions in our human and experimental post-anæsthetic cases falls into line with the observations made by many workers in various types of anoxia. There are some as yet unexplained differences in detail: the globus pallidus seems to be more often selectively affected in carbon monoxide poisoning than in any other type of anoxia. Involvement of the globus pallidus is practically unknown in irreversible hypoglycæmic coma, although striatal lesions are quite common, and this is also the case in epileptic brains despite frequent sclerosis of the cornu ammonis.

The thalamus, apart from its occasional involvement in epileptic brains (Scholz, 1951), has not figured prominently among the vulnerable centres in anoxia. The severe necrosis in this area in three of the human cases described in this paper deserves, therefore, special mention. Fig. 1 demonstrates the lesion in Case V. In this case, the acute necrosis was almost total except for some sparing of the reticular, intralaminary and midline nuclei. There was an equally total necrosis of the striate body extending even into the claustrum. We have observed thalamic necrosis also in other types of anoxia. In a case of delayed death after hanging with survival of three days, for instance, putamen and globus pallidus showed only minimal damage, while the thalamus was severely necrosed, again with distinct sparing of reticular, intralaminary and mid-line nuclei (Fig. 2). There was, in this case, together with other typical lesions, a necrosis of the latero-basal aspect of the amygdaloid nucleus (Fig. 2). This is of interest, in the light of recent findings in epileptic brains, in which sclerosis of this centre has been reported to be associated with that of Ammon's horn (Meyer and Beck, 1955).

The reticular zone of the substantia nigra has been found damaged in some of our human and experimental postanæsthetic cases. Similar findings have been recorded after carbon monoxide and cyanide poisoning. Although the reticular zone is both anatomically and histochemically closely related to the globus pallidus, the incidence of its necrosis is much lower than that of the globus pallidus. Nevertheless, in one case of experimental cyanide

FIG. 1.—Case V of Table I. Ischæmic necrosis of thalamus, striate body and claustrum. Insula shows laminary necrosis of third layer, otherwise normal staining. Nissl stain. × 2.

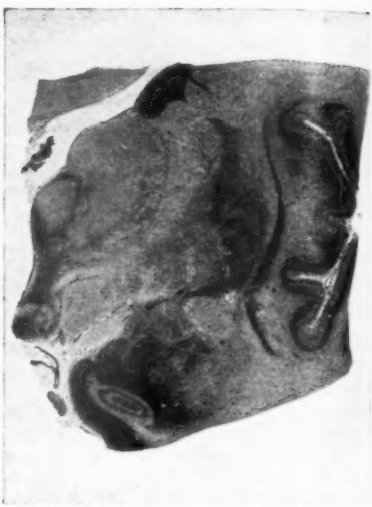


FIG. 2.—Delayed death after hanging. Note thalamic necrosis; the striate body stains in the normal manner, apart from focal necrosis. Laminary necrosis of third layer in insula. Necrosis of latero-basal part of amygdaloid nucleus. Nissl stain. × 1·5.

poisoning a bilateral selective softening of the reticular zone was the only important change in the brain (Meyer, 1933). In two similarly poisoned carnivores, on the other hand, a bilateral softening of the globus pallidus was noticed, entirely sparing the reticular zone.

These facts emphasize the complexity of the problem. If there is a pattern of selective vulnerability to anoxia, it is likely to depend not on one but several factors which may vary not only with different types, but occasionally in an almost freakish manner, even within the same type of anoxia. The direct effect of oxygen-want upon the nervous tissue is probably one important factor. Others arise from the repercussion of oxygen-want upon the circulation resulting—to varying degrees—in capillary and venous stasis, increased permeability of vessel walls, œdema and raised intracranial pressure. Increased cerebral activity at the critical period, as it occurs in states of motor excitement or in epileptic discharges, may also have a determining influence upon the site of lesions.

The latest contribution to the problem of selective vulnerability has been made by Lindenberg (1955), who, from experience in head injuries, is inclined to explain most of the selective lesions by the local pressure which some arterial systems undergo during conditions of increased intracranial pressure. Arteries running close to the tentorial edge (such as the anterior choroidal, posterior cerebral, and superior cerebellar) or which may be pressed against the falx (branches of anterior cerebral) or bone (the stem of the middle cerebral, inferior cerebellar arteries, &c.) are particularly exposed. All terminal branches which supply cerebral or cerebellar cortex in the depths of sulci are similarly vulnerable. Lindenberg's views fall into line with the herniation theory of Earle *et al.* (1953), in temporal lobe epilepsy, and, to some extent at least, with views expressed by the present writer and his associates (Meyer, 1939; Meyer *et al.*, 1954; Meyer *et al.*, 1955). Although a detailed critical assessment of Lindenberg's paper must be reserved for a later occasion, it undoubtedly deserves close attention in the further discussion of this difficult problem.

REFERENCES

BEDFORD, P. D. (1955) *Lancet*, ii, 259.

EARLE, K. M., BALDWIN, N., and PENFIELD, W. (1953) *Arch. Neurol. Psychiat., Chicago*, **69**, 27.

HOWKINS, J., MCLAUGHLIN, C. R., and DANIEL, P. (1946) *Lancet*, i, 488.

LINDENBERG, R. (1955) *J. Neuropath.*, **14**, 223.

MEYER, A. (1933) *Z. ges. Neurol. Psychiat.*, **143**, 333; (1939) *J. ment. Sci.*, **85**, 927.

——, and BECK, E. (1955) *Proc. R. Soc. Med.*, **48**, 457.

——, ——, and SHEPHERD, M. (1955) *J. Neurol. Psychiat.*, **18**, 24.

——, and BLUME, W. (1934) *Z. ges. Neurol. Psychiat.*, **149**, 678.

——, FALCONER, M. A., and BECK, E. (1954) *J. Neurol. Psychiat.*, **17**, 276.

SCHOLZ, W. (1951) Die Krampfschädigungen des Gehirns. Berlin.

Section of Medicine

President—G. E. BEAUMONT, M.A., M.D., F.R.C.P., D.R.H.

[*February* 28, 1956]

DISCUSSION: DIURESIS AND DIURETICS

Dr. D. A. K. Black (Dept. of Medicine, Manchester University) :

On the Continent, "diuresis" can be taken as synonymous with urine flow-rate; whereas in this country and in America it implies an increase in urine flow, either "spontaneous" or in response to a stimulus. It may be worth while to keep both these definitions in mind; for an understanding of the factors which normally determine urine flow is helpful in seeing when these are deficient in disease, and in devising substitute-mechanisms to replace them.

On current theories of renal function, we can distinguish three main determinants of urine flow-rate.

(1) The "filtered load" of water and solutes, which greatly exceeds the urine volume, but which can be significantly depressed when the renal circulation is reduced.

(2) The "facultative reabsorption" of water in the distal tubule, whose rate is mainly controlled by the anti-diuretic hormone of the posterior pituitary, but is also influenced by cortisone in patients with adrenal insufficiency.

(3) The tubular reabsorption of sodium and its associated anions which is enhanced by aldosterone.

Borst and deVries (1950) distinguished three forms of "natural diuresis"—water diuresis, osmotic diuresis, and the diurnal variations in urine-flow. Many of us think that diurnal variation may be a special case of osmotic diuresis (Stanbury and Thomson, 1951). The distinction between water diuresis and osmotic diuresis is an important one in practice; our object in diuretic treatment is to eliminate solutes from the body as well as water, and this will not be achieved by inducing a pure water diuresis. In a water diuresis, the *concentration* of solutes in the urine falls off with increasing urine volume until the specific gravity of the urine is almost that of water; the *rate* of solute excretion changes little if at all. In an osmotic diuresis, induced by a "loading solute" such as mannitol or urea, the *concentration* of total solutes also decreases with increasing urine volume, but falls only to a level comparable to the solute concentration in plasma; the *rate* of solute excretion increases, as it must do to eliminate the imposed load of solute.

Oliguria in itself is not an indication for the use of conventional diuretic agents. When oliguria is related to acute renal failure, diuretic drugs are ineffective and may be harmful. When oliguria is due to inadequate renal blood-flow, the prime indication is to restore the circulation by transfusion of blood or plasma in surgical shock; by giving sodium-containing solutions in sodium depletion; and by rest and general treatment in cardiac failure. Oliguria due to maximal water reabsorption under the influence of A.D.H. is usually transient, and does not lead to significant solute retention; oliguria in adrenal insufficiency, anæmia, and steatorrhœa responds to effective treatment of the primary disease, and does not require diuretics.

The real indication for treatment with diuretics is a combination of oliguria and œdema, which implies retention of solutes, namely sodium and its accompanying anions. With this is retained enough water to prevent increase in the osmolarity of extracellular fluid; this secondary increase in body water is accomplished partly by the thirst mechanism and partly by A.D.H. The clinical situation may be further complicated by hypoproteinæmia or urea retention; but the abnormality most susceptible to diuretic treatment is the retention of sodium. To get rid of this, we must induce an osmotic diuresis, either by increasing the filtered load of sodium, or indirectly by decreasing the tubular reabsorption of sodium.

The filtered load of sodium can be increased by any measure which increases renal plasma flow, and the xanthine diuretics probably act in this way: the osmotic diuretics, such as mannitol, dextran, and urea may also increase sodium filtration, though their main action is to depress tubular reabsorption of sodium. Salt-free albumin infusions increase the filtered load of sodium effectively, but transiently; a high-protein diet is more practicable, but less effective.

The most effective group of diuretics which we possess, the organic mercurials, do not appreciably affect the filtered load of sodium; but they partly inhibit sodium reabsorption, not directly, but by inhibiting chloride reabsorption. Increase in anion excretion can also be effected by the carbonic anhydrase inhibitors, and by acidifying salts such as ammonium chloride.

In the ensuing discussion, I have little doubt that the limitations as well as the usefulness of currently available diuretics will be stressed. Failure to achieve diuresis and resolution of œdema is no doubt often due to the renal circulation being hopelessly compromised by

cardiac failure; but sometimes the renal tubules seem to be reabsorbing sodium with abnormal avidity under the influence of aldosterone. Even adrenalectomy has been resorted to in obstinate œdema; but the future may bring some less desperate method of preventing aldosterone production, or of blocking its action on sodium reabsorption.

REFERENCES

BORST, J. G. G., and DEVRIES, L. A. (1950) *Lancet*, ii, 1.
STANBURY, S. W., and THOMSON, A. E. (1951) *Clin. Sci.*, **10**, 267.

Dr. T. Hanley: *The Diuretic Action of Acetazolamide*

Acetazolamide (the official name for "Diamox") is a powerful inhibitor of the enzyme carbonic anhydrase (Miller, *et al.*, 1950). It is believed that the renal tubule cells reabsorb "bicarbonate-bound base" by exchanging sodium ions contained in the glomerular filtrate for hydrogen ions which have been formed within the cells from carbon dioxide hydrated under the catalytic influence of this enzyme (Pitts and Alexander, 1945). Inhibition of carbonic anhydrase thus causes excretion of a proportion of the "filtered load" of bicarbonate, and the diuretic action of acetazolamide is largely dependent on the osmotic effect of this augmented excretion of bicarbonate. When the drug is administered in therapeutic dosage (0·25 to 1·0 gram) at intervals of twenty-four hours or more frequently, its action is transient. By the third or fourth day the acid-base composition of the urine returns to normal, bicarbonate excretion ceases and no further diuresis occurs. This diminishing effect limits very considerably the therapeutic effect of the drug. It appears probable that the development of "resistance" to the action of acetazolamide is induced automatically by the fall of plasma bicarbonate concentration which results from loss of bicarbonate in the urine (Counihan, Evans and Milne, 1954; Hanley and Platts, 1956). Complete "resistance" to the drug's action is associated with reduction of the load of bicarbonate filtered by the glomeruli to about 75% of the initial level, and this occurs when approximately 200 milli-equivalents of bicarbonate have been lost in the urine. Continued administration of the drug beyond this point will maintain depression of the plasma bicarbonate and a systemic acidosis, but will not cause any further urinary excretion of bicarbonate.

In a clinical trial of acetazolamide on 18 patients with congestive heart failure of various ætiology Hanley and Platts (1956) observed a good therapeutic effect in only 3 instances, and the remaining 15 patients were still œdematous after several days of treatment with acetazolamide (0·25 to 1·0 gram daily or on alternate days). Comparison of the diuretic effect of mersalyl B.P. and acetazolamide on 15 of these persons showed that, in general, the mercurial diuretic caused a much larger increment of sodium and water excretion and a considerably greater reduction of œdema and venous pressure than did acetazolamide. The carbonic anhydrase inhibitor was also administered to 12 patients who had recently recovered from an attack of congestive heart failure and who were free from œdema when therapy was begun. 5 of these 12 patients again developed œdema and venous congestion within four to eight weeks. No serious toxic symptoms were observed in any patient, although many complained of drowsiness, headache and paræsthesiæ. There was no clinical evidence of potassium deficiency even in those patients treated for continuous periods of a few months to one year. The general conclusion was reached that acetazolamide compares unfavourably with the mercurial diuretics in the treatment of congestive heart failure, and that reliance should not be placed on acetazolamide alone for relief of œdema. Occasionally a good therapeutic result may be obtained from the drug but it does not seem possible to predict on which patients this will occur. Acetazolamide may, however, prove to be an effective adjuvant to mersalyl therapy by correcting the hypochloræmia which is, in some instances, associated with "resistance" to mercurials, and this aspect of the drug's action merits further investigation. In the prophylaxis of cardiac œdema acetazolamide has not proved to be very effective, and it seems improbable that it will supplant the well-established mercurial diuretics in this respect.

REFERENCES

COUNIHAN, T. B., EVANS, B. M., and MILNE, M. D. (1954) *Clin. Sci.*, **13**, 583.
HANLEY, T., and PLATTS, M. M. (1956) *J. Clin. invest.*, **35**, 20.
——, —— (1956) To be published.
MILLER, W. H., DESSERT, A. M., and ROBLIN, R. O., Jr. (1950) *J. Amer. Chem. Soc.*, **72**, 4893.
PITTS, R. F., and ALEXANDER, R. S. (1945) *Amer. J. Physiol.*, **144**, 239.

Dr. M. D. Milne: *Mercurial Diuretics*

Acetazolamide partially inhibits reabsorption of bicarbonate by the renal tubules, and therefore increases the rate of excretion of this anion. Mercurial diuretics have a comparable action in increasing the rate of chloride excretion. There are, however, important quantita-

tive differences in the action of these diuretic drugs (Table I). The concentration of chloride in plasma is almost four times as great as that of bicarbonate, and therefore the glomerular filtrate contains considerably more chloride than bicarbonate. The maximal diuretic effect of mercurials results in an excretion of only 20% of the filtered chloride (Duggan and Pitts, 1949), and similarly, therapeutic doses of acetazolamide produce a maximum rate of bicarbonate excretion of 25% of the amount filtered (Counihan *et al.*, 1954). Consequently, mercurial diuretics are potentially three times more effective than acetazolamide (Table I).

TABLE I.—QUANTITATIVE ASPECTS OF CHLORIDE AND BICARBONATE EXCRETION

Plasma chloride × glomerular filtration rate
= amount of chloride filtered at the glomeruli each minute.
0·1 mEq./ml. × 120 ml./min. = 12·0 mEq. Cl/min.

Maximum excretion rate after a mercurial injection is 20% of filtered chloride
= 2·4 mEq. Cl/min.

Plasma bicarbonate × glomerular filtration rate.
= amount of bicarbonate filtered at the glomeruli each minute.
0·027 mEq./ml. × 120 ml./min. = 3·24 mEq. bicarbonate/min.

Maximum excretion rate after ingestion of a therapeutic dose of acetazolamide is 25% of filtered bicarbonate.
= 0·81 mEq. bicarbonate/min.

Therefore the maximum effect of a mercurial is about three times the maximum effect of acetazolamide.

The increase of urinary anion necessarily results in a corresponding rise of urinary cation, which is almost entirely sodium and potassium in varying proportion. Increased output of sodium is beneficial, but potassium loss is an undesirable complication of diuretic therapy. Secondary potassium depletion is particularly harmful in congestive heart failure since it increases digitalis toxicity (Lown *et al.*, 1951). The higher the proportion of sodium excreted in relation to potassium, the more efficient is the diuretic agent. Significant potassium loss is found in states of "secondary aldosteronism" where there is a stimulus to the adrenals to secrete excess aldosterone. This occurs after dietary sodium depletion or increased potassium intake, and in severe congestive heart failure, cirrhosis of the liver with ascites, and the nephrotic syndrome with massive œdema (Luetscher and Curtis, 1955). Representative values of the proportions of sodium and potassium output after acetazolamide and mercurial diuretics are given in Table II (data from paper of Counihan *et al.*, 1954). It is

TABLE II.—PROPORTIONS OF EXCESS SODIUM AND POTASSIUM OUTPUT AFTER MERCURIAL DIURETICS AND ACETAZOLAMIDE
(the data are taken from Counihan *et al.*, 1954)

	Mercurial diuretics		Acetazolamide	
State of subject	Excess Na %	Excess K %	Excess Na %	Excess K %
Potassium depletion			92%	8%
Normal subjects	95%	5%	68%	32%
Severe congestive heart failure	73%	27%	Zero	100%

seen that the proportion of potassium is invariably higher after acetazolamide than after mercurials. Acetazolamide produces an alkaline urine which favours excess potassium exchange for sodium (Berliner *et al.*, 1951). The greatest potassium loss occurs in grave congestive heart failure with severe secondary aldosteronism. Acetazolamide in such cases may cause an increased output of potassium bicarbonate alone, no excess sodium being eliminated. This may be misleading if the efficiency of the diuretic is assessed solely by increase of urinary volume without analyses of urinary sodium and potassium. Similar results have been reported in cases of the nephrotic syndrome (Metcoff *et al.*, 1955), and in hepatic cirrhosis with ascites (Hecker, 1956). Potassium deficiency can be avoided by the routine use of potassium supplements in all patients receiving regular diuretic therapy. Potassium chloride should be used with mercurials, and potassium bicarbonate or citrate with acetazolamide.

Both mercurial diuretics and acetazolamide have a self-limiting action due to alteration in plasma composition. Mercurials cause a reduction of plasma chloride with increase of plasma bicarbonate, i.e. a hypochloræmic alkalosis. Acetazolamide has the opposite effect with production of a hyperchloræmic acidosis. The single greatest disadvantage of acetazolamide as a diuretic lies in the difficulty of correcting the acidosis with restoration of the

diuretic effect. Administration of sodium bicarbonate would defeat the object of therapy, i.e. elimination of sodium. The use of potassium bicarbonate is also ineffective since potassium exchange for sodium is increased with consequent excretion of potassium bicarbonate rather than sodium bicarbonate. In contrast, there are three methods of correction of the hypochloræmic alkalosis produced by mercurials and thus the diuretic effect can be maintained. Ammonium chloride, cation exchange resins in the ammonium cycle, and acetazolamide itself, all produce an acidosis with increase of plasma chloride and are therefore valuable adjuvants to mercurial diuretics. Acetazolamide is more useful as a means of potentiating the action of mercurials than as a diuretic in its own right.

As a general rule, the effect of mercurials is roughly proportional to the amount of chloride filtered at the glomeruli, i.e. the product of plasma chloride and glomerular filtration rate. The plasma chloride can be increased by use of ammonium chloride, exchange resins, or acetazolamide as already described. The patient may still, however, prove refractory to mercurials if the glomerular filtration rate is grossly reduced, as in severe congestive heart failure. In such cases sensitivity may sometimes be restored by intravenous aminophylline which causes a temporary increase of glomerular filtration rate (Vogl and Esserman, 1951). Aminophylline at a maximum dose of 0·5 gram intravenously is best given about two hours after the intramuscular injection of the mercurial when the greatest synergistic action is obtained. Mersalyl contains some aminophylline but in insufficient amount to provide this particular effect. Mudge and Hardin (1956) have recently described an important exception to the general rule that the effect of mercurials is roughly proportional to the amount of chloride in the glomerular filtrate. They found that an excellent diuresis occurred in potassium depletion with hypokalæmic alkalosis and low plasma chloride. The renal tubular cells in potassium depletion are abnormally acidic (Anderson and Mudge, 1955), and it was thought that intracellular acidity increases the dissociation of mercury and thus potentiates the diuretic effect.

Mercurial diuretics are relatively non-toxic even when given for prolonged periods. One patient is known to have received 627 injections in twelve years without showing any evidence of toxic effect (Friedenson, 1944). Two cases are recorded who had received large doses of mercurials at weekly intervals for many years without any renal damage or biochemical evidence of retention of mercury being found at necropsy (Schroeder, 1951). Normally, 75% to 95% of the mercury is excreted within the first twenty-four hours after injection, and elimination is virtually complete within three days (Burch *et al.*, 1950). Toxic effects from accumulation of mercury will therefore occur only in patients showing inefficient and delayed excretion. This may be found in cases with gross reduction of the glomerular filtration rate and increase of blood urea, and in refractory individuals without a significant diuretic response. Mercurials are therefore contra-indicated in uræmia and in patients who are consistently refractory despite administration of the adjuvants previously described. A large proportion of the mercury temporarily accumulates in the outer parts of the renal cortex (Greif *et al.*, 1956), and therefore renal damage may occasionally occur. Proteinuria and oliguria with increasing uræmia are the most common signs of renal damage. Dimercaprol (BAL) is useful in preventing further damage and increasing the rate of mercury excretion. Munck and Nissen (1956) have recently claimed that organic mercurials can occasionally cause a true nephrotic syndrome. No evidence of accumulation of mercury was obtained in the four cases described, and therefore the evidence is incomplete. Mercurial diuretics are not necessarily contra-indicated in patients with proteinuria. Many cases of congestive heart failure are complicated by proteinuria which often disappears with therapy. Increasing urinary protein loss is, however, a sign of renal damage and an indication to stop diuretic therapy.

REFERENCES

Anderson, H. M., and Mudge, G. H. (1955) *J. clin. Invest.*, **34**, 1691.
Berliner, R. W., Kennedy, T. J., and Orloff, J. (1951) *Amer. J. Med.*, **11**, 274.
Burch, G., Ray, T., Threefoot, S., Kelly, F. J., and Svedberg, A. (1950) *J. clin. Invest.*, **29**, 1131.
Counihan, T. B., Evans, B. M., and Milne, M. D. (1954) *Clin. Sci.*, **13**, 583.
Duggan, J. J., and Pitts, R. F. (1949) *Fed. Proc.*, **8**, 37.
Friedenson, M. (1944) *Ann. intern. Med.*, **20**, 306.
Greif, R. L., Sullivan, W. J., Jacobs, G. S., and Pitts, R. F. (1956) *J. clin. Invest.*, **35**, 38.
Hecker, R. (1956) Personal communication.
Lown, B., Salzberg, H., Enselberg, C. D., and Weston, R. E. (1951) *Proc. Soc. exp. Biol., N.Y.*, **76**, 797.
Luetscher, J. A., and Curtis, R. H. (1955) *Ann. intern. Med.*, **43**, 658.
Metcoff, J., James, J. A., Gordillo, G., and Antonowicz, I. (1955) *J. Lab. clin. Med.*, **46**, 333.
Mudge, G. H., and Hardin, B. (1956) *J. clin. Invest.*, **35**, 155.
Munck, O., and Nissen, N. I. (1956) *Acta. med. scand.*, **153**, 307.
Schroeder, H. A. (1951) *Circulation*, **4**, 87.
Vogl, A., and Esserman, P. (1951) *J. Amer. med. Ass.*, **147**, 625.

JOINT MEETING No. 3

Section of Medicine with Section of Proctology

Chairman—G. E. BEAUMONT, M.A., D.M., F.R.C.P., D.P.H.
(President of the Section of Medicine)

[*March* 27, 1956]

DISCUSSION: THE DIAGNOSIS AND INVESTIGATION OF CHRONIC DIARRHŒA (EXCLUDING TROPICAL DIARRHŒA)

Dr. W. Trevor Cooke: Diarrhœa is the passage of an unformed stool and may vary considerably in volume, in some cases up to a litre being passed at one time. It is characterized by an increased water content, increased sodium content and sometimes by an increased content of potassium. The normal stool is passed once or twice a day, is formed and contains 100–200 ml. of water, 2–5 mEq. of sodium and 10–20 mEq. of potassium together with 20–30 grams of solids. With increase of diarrhœa, sodium appears to bear a direct relationship to the water content, as much as 200 mEq. being excreted with 2 litres of fluid per day, though potassium does not bear any close relationship and is not excreted in such large quantities as sodium. The adjective "chronic" may be considered to apply to those diarrhœas not acute and either continual or recurrent. It must be recalled and emphasized, however, that what the doctor might class as chronic diarrhœa is often accepted by the patient as being a normal part of his daily habits and only specific questioning will reveal the presence of chronic diarrhœa and so lead to the elucidation of its cause for the proper treatment of the patient.

The causes of chronic diarrhœa have been classified according to whether they are due to disorders of the stomach, small intestine or colon, or of systemic cause. While this classification is helpful in an empirical way, it offers no intellectual satisfaction as to why these causes should give rise to diarrhœa. It is self-evident that whether or not the given patient has diarrhœa will depend upon the function of the colon alone, and that even some of the most severe disturbances of small intestinal and gastric function may be associated with normal stool consistency. If the discharges from a normal ileum following ileostomy are any guide to the normal daily discharge of ileal contents into the colon, then large volumes of water up to 2 litres or more a day containing sodium in at least isotonic concentration and sometimes being as high as 800 mEq. in the 24 hours are presented to the colon for re-absorption each day (Brooke, 1956). It has generally been accepted that this remarkably efficient re-absorption of sodium and water takes place principally in the ascending colon. There are, however, many clinical observations which suggest that the whole of the colon takes part in this active re-absorption and it is probable that every part of the colon can accommodate to active water and electrolyte re-absorption when necessary. Since sodium and water bear some constant and close relationship to each other, it does not need much upset in the re-absorptive function of the colon to produce a diarrhœic stool.

Causes for diarrhœa may, therefore, be sought in the conditions that bring about in particular,

(1) alterations in the fluids presented to the colon making them either hypertonic or otherwise irritant to the mucosa,

(2) destructive processes in the wall of the colon itself,

(3) alterations in the neuro-muscular and vasomotor tone of the colon brought about by (*a*) constitutional factors, e.g. psychomotor or thyrotoxic, (*b*) local factors, amongst which lesions such as polypi, external adhesions affecting particularly the sigmoid flexure and external pressure of such disorders as uterine and ovarian tumours, may be cited.

I shall deal particularly with the group which results in alterations in the normal ileal contents subsequently causing the colon to produce a diarrhœic stool. I am not proposing to consider the clinical history of a patient with chronic diarrhœa in detail even although it may be diagnostic in some instances.

Methods of Investigation

(1) Inspection of the stool: Inspection of the stool is probably one of the most neglected procedures in clinical medicine yet often it will give clear evidence where the source of the trouble is to be found e.g. in the small intestine, with the bulky pale stools of some patients with steatorrhœa, presence of undigested food. Stools with an aluminium sheen are seen when steatorrhœa is due to causes other than carcinoma of the ampulla of Vater and have no specific diagnostic connotation.

(2) Microscopical examination: This should be practised routinely. The presence of undigested meat fibres, fat globules, fatty acid crystals, pus, red cells, *Giardia lamblia* or

other intestinal protozoa should be looked for. Increased concentration of fatty acid crystals is common in the presence of steatorrhœa and with the history of chronic diarrhœa indicates the need for further chemical analysis of the fæces. However, neither the presence of excess fatty acids nor their absence is any guide as to the presence or absence of steatorrhœa. Muscle fibres can be seen in virtually any chronic diarrhœa but the persistence of fibres when the stools have been standing twenty-four hours suggests pancreatic deficiency. Stress has been laid on the presence of starch granules, but I myself have not gained much information of clinical value from them.

Chemical Analysis of the Fæces

Analysis of the fæces for fat content has now become essential for accurate diagnosis and the presence of an increased fat content is diagnostic of small intestinal dysfunction but has no further ætiological significance. Determination of the percentage fat (dried weight) in a portion of daily fæces has now largely been abandoned, although percentages over 30 are only rarely to be found in patients who do not have steatorrhœa. Differential analysis of the amount of split and unsplit fat in the fæces is rarely used for it is no longer regarded as valid evidence as to the presence or absence of pancreatic dysfunction. In fact, the only use that I can see for the test is to provide a check on ward routine so that false answers are not obtained through the unwitting administration of liquid paraffin.

Many hospitals have been deterred from fæcal fat analyses on the grounds that careful balance techniques are necessary and not so long ago the administration of a diet containing a known amount of fat usually 50 or 70 grams was considered essential and the resultant daily fat excretion could then be expressed in terms of the amount of daily fat absorption. It has, however, come to be recognized that such expressions give a false impression of scientific accuracy. Further a normal individual on diets containing fat varying between 50 and 120 grams of fat a day rarely excretes more than 6 grams in any one day, and in my experience, the mean varies only slightly on increasing loads of fat rising from 2·8 to 3·5 grams per day. It follows from this that for diagnostic purposes it is permissible to analyse daily fæcal fat excretion in a patient on a normal varied diet and that an average daily excretion for 3–5 days of over 6 grams per day may be taken to indicate small intestinal dysfunction or steatorrhœa. The use of an electric mixer, a good refrigerator and simpler methods of analysis make it possible for even the smallest laboratory to carry out fat estimations with adequate accuracy for the investigation of any case of chronic diarrhœa.

Nitrogen

For diagnostic purposes, there is little point in estimating the daily fæcal nitrogen excretion. Increased nitrogen content of over 2 grams per day has often been taken to indicate pancreatitis. It has, however, been pointed out by a number of workers that almost any diarrhœa will lead to an increased fæcal nitrogen. As far as the diarrhœa associated with steatorrhœa is concerned, the more fat the more nitrogen whether the steatorrhœa be of idiopathic or pancreatic origin.

In the investigation of chronic diarrhœa, a careful radiological examination is important, particularly in those patients in whom the small-intestine lesions have brought about the chronic diarrhœa. It is time-consuming and entails frequent films and much screening but unless some indication can be given to the radiologist as to what exactly is being looked for, such examinations may lead only to waste of the radiologist's and patient's time, to say little of the expense of films involved. For routine purposes, I have been accustomed to ask for a poorly flocculating barium contrast medium, such as Raybar, since areas of dilatation or inflammation as in jejuno-ileitis are more readily delineated, while should flocculating occur then that in itself is good evidence of dysfunction of the small intestine. However, if barium sulphate and water suspensions are used, then flocculation must be accepted as indicating excess mucus in the intestinal lumen and usually indicates the presence of steatorrhœa. It may not always do so, since, for example, some 7% of patients with pernicious anæmia present with chronic diarrhœa and occasionally some have extensive flocculation but no steatorrhœa. Any patient who has a scar on his abdomen and suffers with chronic diarrhœa deserves careful radiological examination of the intestinal tract, so that the normal continuity of the gut can be established and the existence of any blind loop excluded.

The importance of hæmatological investigation must not be overlooked for many disorders of the small intestine are associated with macrocytic anæmia, as has been discussed at a recent meeting of the Society (Witts, 1955).

As aids to diagnosis the use of both glucose tolerance tests and chylomicrographs is disappointing owing to the wide range of results obtained in any particular disorder. Culture examination of the fæces can also provide further evidence of the ætiology of certain types of chronic diarrhœa. The role of the pathogenic staphylococcus is, however, by no means clear, whilst the *Giardia lamblia* is usually rejected as a significant factor even though patients so infected may have their diarrhœa cleared by the administration of mepacrine. The

role of fungi and yeasts still remains to be clarified and little has been reported in this country on the possible association of histoplasmosis and enterocolitis.

In conclusion, the prerogative of an opening speaker allows a few dogmatic comments on some of the traditional causes of diarrhœa. The diagnosis of lienteric diarrhœa or diarrhœa associated with achlorhydria should now be discarded. There is no satisfactory evidence that achlorhydria is prone to give diarrhœa or to cause rapid gastric emptying. Many of the patients to whom this diagnosis is attached will prove to have steatorrhœa and in others the basis will be psychological. Gastro-intestinal hurry is much favoured as a cause for diarrhœa. The evidence, however, on which this is based is poor. The difficulties in measuring the transit time through the small intestine are great, for visualization of the rate of passage of barium does not guarantee that food travels at the same rate. The diarrhœas following gastrectomy that I have studied showed the rate of barium transit through the small intestine to be longer rather than shorter. The third diagnosis which may be queried is that of tabes mesenterica or mesenteric lymphadenopathy; in my experience neither of these two conditions gives rise to chronic diarrhœa unless the intestinal wall itself is involved in the disease processes.

REFERENCES

BROOKE, B. N. (1956) *Proc. R. Soc. Med.*, **49**, (in press).
WITTS, L. J. (1955) *Proc. R. Soc. Med.*, **48**, 248.

Mr. W. M. Capper:

Diarrhœa of gastric origin.—Gastrogenous diarrhœa in general is usually distinguished by the fact that it occurs very soon after a meal and often in the early morning hours. It tends to affect patients in the mid-life or beyond, and evacuations rarely exceed six in a day: indeed, they are usually less. Stools are soft and mushy, not watery; there is no blood, pus, or mucus, and the patients may say that they cover the pan. Motions are usually unaccompanied by pain and may be intermittent in character, i.e. they are frequent for two or three days and then are better perhaps for five or more days, when the diarrhœa will again recur. Attacks may be associated with the intake of specific food such as hot sweet nutrient liquids, or possibly by fried or highly spiced foods. The stools may contain recognizable food particles from the last meal. Gastrogenous diarrhœa may be divided as to causation into two main groups: those cases which follow surgery on the stomach, and those that occur entirely apart from any surgery at all.

(1) *Diarrhœa following Gastric Surgery*

(*a*) *Following total gastrectomy.*—Welbourn (1956) found diarrhœa present in 3 out of 9 patients surviving one year or more. Re Mine and Priestley (1952) followed up 13 patients who had survived five or more years, and found that diarrhœa was "infrequent". Of my own cases, it has not been troublesome in more than 1 out of 6 surviving longer than two years. It has the classical features of gastrogenous diarrhœa and barium meal usually shows intestinal hurry.

(*b*) *Following partial gastrectomy.*—This occurs in 3 main groups—(i) Diarrhœa may occur on the third to fifth day after operation when solid food first starts to be taken. It is noticeably worse in cases when operation has been carried out for pyloric stenosis, especially if adequate pre-operative lavage has not been performed. It usually consists of anything up to ten stools a day and must be closely observed in case the features of a severe enterocolitis supervene. It has been stated that it will respond to hydrochloric acid by mouth or to antibiotics, but I have not found either of these measures to be effective. It usually subsides without special treatment beyond frequent small doses of I-so-gel.

(ii) Severe and sometimes fatal enterocolitis may appear about the second post-operative day. In 35 cases out of 1,700 partial gastrectomies reported by Dawson-Edwards and Morrissey (1955) 5 were fatal. Profound shock and incessant diarrhœa are the main diagnostic features and resuscitative treatment must be instituted immediately. This condition has assumed importance recently since it has been realized it is an important factor in any series of deaths following partial gastrectomy.

(iii) In a few cases, a low-grade diarrhœa starts after partial gastrectomy and persists. Frank steatorrhœa with bulky and offensive stools is rare, but many patients have an excess of fat in their fæces. Welbourn (1953) investigated 248 cases of partial gastrectomy, most of which were a 70% Polya, and found that 110 (i.e. 44%) noticed that their bowels were more regular, and 9 of these (4%) developed diarrhœa for the first time. B. N. Brooke (1954) found 9 out of 167 cases (i.e. 5%) followed a Polya operation. He found no cases out of 48 who had a Billroth I operation. Bohmansson (1926) found that there were intestinal disturbances in 24% of cases after the Polya operation, and 6% after the Billroth operation. Of my own cases, 3% of Polya cases complained of loose stools which tend to follow meals, and are sometimes explosive in character. They may, or may not, be associ-

ated with the dumping syndrome or biliary vomiting. Glazebrook and Welbourn (1952) found that barium meal in these cases shows unusually rapid intestinal passage and kymography reveals excessive peristaltic activity. Very rarely X-rays may actually show a reduction of activity with clumping of the barium, although there is complaint of diarrhœa (Glazebrook, 1952; MacPhee, 1953). It seems definite that symptoms are commoner following a Polya anastomosis and there is usually increased fat in the stools. The probable cause is excessive bowel mobility following the entry of food into the jejunum. The symptoms can usually be relieved by the exhibition of ganglion-blocking drugs such as propantheline bromide and hexamethonium.

(*c*) *Following gastro-enterostomy.*—Diarrhœa may follow this operation exactly as in partial gastrectomy, but is unusual.

(*d*) *Following vagotomy.*—This operation when it is done as a solitary procedure gives rise to a combination of achlorhydria and pylorospasm. The infected pent-up gastric contents pass into the jejunum from time to time. They are highly irritating and give rise to diarrhœa which may be quite severe in character. The condition usually ceases when the stomach is drained by a pyloroplasty or gastrojejunostomy.

(*e*) *Gastro-jejuno-colic fistula.*—This must always be borne in mind as a possible cause of diarrhœa in any patient who has had a gastro-enterostomy. Indeed, in such a case it is usually right to assume that such a fistula is present until there is absolute proof that it is not so. Classically, the story is that after an interval of months or years, following a gastrojejunostomy, there is a brief period when typical symptoms of anastomotic ulcer are present. The patient then says that the persistent indigestion has suddenly ceased, and is replaced by incessant diarrhœa and belching of foul gas. Clinically this is followed by progressive cachexia, hypoproteinæmia, and a deficiency state with steady decline. The stools are sprue-like and there may be fæcal vomiting. In certain cases, depending on the size of the fistula, there may be no symptoms relating to the bowel. Lowdon (1953) found diarrhœa as the main symptom in 41 out of 46 cases. The severity varied from 4 to 20 or 30 stools a day. In some cases there was incontinence of a watery fluid. Fæcal vomiting occurred in 25, and wasting in 36, out of the 46 cases. It may be difficult to prove the diagnosis. In a barium meal the medium often does not pass into the bowel via the fistula. A barium enema revealed the lesion in 31 out of 32 cases (Lowdon, 1953). If the fistula is small, an enema of aqueous methyl carmine with an in-dwelling stomach tube may show dye in the gastric washings. It is also worth while to have an in-dwelling stomach tube when the barium enema is given, to see whether there is any barium in the washings. Uncertainty in the diagnosis must not be allowed to delay laparotomy, as these patients may decline rapidly and their condition become precarious. Adequate and efficient surgery becomes then a life-saving measure.

(2) *Gastrogenous Diarrhœa not associated with Surgery*

Various writers have described diarrhœa as secondary to achlorhydria but it certainly is not common. In my experience a patient with alcoholic gastritis usually has one or two loose stools in the morning and then is not generally bothered for the rest of the day. Bockus (1946) says that diarrhœa occurs in 10% of cases of achlorhydria. Amongst the causes, he quotes pernicious anæmia, hypochromic microcytic anæmia in females and carcinoma of the stomach. The attacks in susceptible patients are often precipitated by eating large amounts of roughage or indulgence in alcohol. One of my colleagues, Mr. Gordon Paul, has recently had a case of pyloric cancer, where the main symptoms were loss of weight and diarrhœa usually occurring just after food. At operation the pylorus was rigid and stenosed but the passage of infected food material through the pylorus was possible, thus causing jejunal irritation and the post-prandial diarrhœa.

It must be emphasized that gastrogenous diarrhœa does not present undue difficulty in diagnosis. The history as given by the patient is usually directed towards the gastric condition, with diarrhœa as a secondary complaint. In cases following gastric surgery, of course, the patient usually volunteers the information that the diarrhœa started after operation and had not occurred before.

REFERENCES

Bockus, H. L. (1946) Gastro-Enterology II. London, p. 545.

Bohmansson, G. (1926) *Acta chir. scand.*, Suppl. 7.

Brooke, B. N. (1954) Personal Communication.

Dawson-Edwards, P., and Morrissey, D. M. (1955) *Brit. J. Surg.*, **42**, 643.

Glazebrook, A. J. (1952) *Lancet*, i, 895.

——, and Welbourn, R. B. (1952) *Brit. J. Surg.*, **40**, 111.

Lowdon, A. G. R. (1953) *Brit. J. Surg.*, **41**, 113.

MacPhee, I. W. (1953) *Lancet*, i, 679.

Re Mine, W. M., and Priestley, J. T. (1952) *Surg. Gynec. Obstet.*, **94**, 519.

Welbourn, R. B. (1953) M.D. Thesis Univ. Camb.

—— (1956) Personal Communication.

Section of Pædiatrics

President—J. VERNON BRAITHWAITE, M.D., F.R.C.P.

[*November* 25, 1955]

[Continued from August *Proceedings*, Page 603]

Heavy Metal Poisoning ? Type.—HUGH JOLLY, M.A., M.D., M.R.C.P., D.C.H.

Michael E., aged 2½ years.

Admitted to hospital on 5.7.55 with a history of vomiting and constipation for nine days. His parents stated that for some time he has had the habit of eating dirt and anything else he can lay his hands on. Examination at this stage showed him to be a reasonably healthy-looking child apart from some pallor and there were no abnormal physical signs. An X-ray of the abdomen showed numerous fine radio-opaque objects in the gut suggesting the ingestion of lead (Fig. 1) but an X-ray of the wrist showed no obvious band of increased density although the appearance of the lower ends of the radius and ulna was suspicious. The hæmoglobin was 60% but there was no punctate basophilia. During five days in hospital the child did not vomit and he was therefore started on iron and discharged to out-patients for further observation.

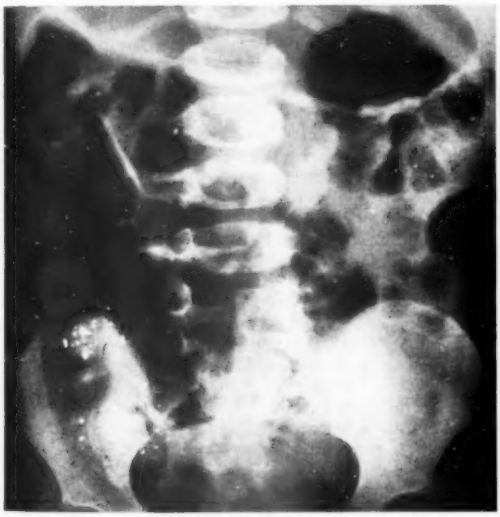


FIG. 1.

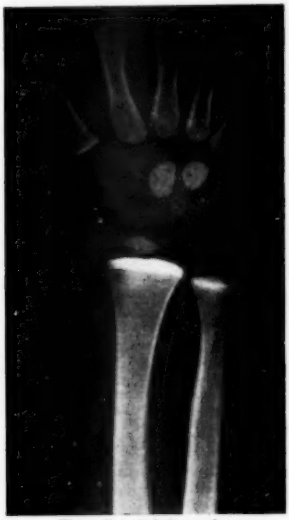


FIG. 2.—Right wrist.

During the next three months he continued to vomit intermittently, the hæmoglobin fell to 50% and an apical systolic murmur appeared. Punctate basophilia was not found despite repeated observations but an X-ray of the wrist now showed a dense line at the lower end of the radius and ulna (Fig. 2). In view of these findings he was readmitted to hospital on 21.10.55 for further investigation. No porphyrins were detected in the urine and two estimations of the urine for lead gave a normal reading of less than 5 microgrammes per cent. The boy was then given intravenous calcium versenate for four days, but the urine passed during this period again contained no lead. X-rays of sweepings from the floor of the boy's home have shown minute radio-opaque objects identical to those seen in the gut.

All the evidence points to the fact that this child's symptoms are the result of poisoning by some heavy metal. However, although lead is the most likely metal, up to date all attempts to prove its presence have failed.

[*February* 24, 1956]

Meeting held at St. Thomas' Hospital, London

Leuco-encephalitis.—Dr. Elizabeth Martin, Dr. C. McCance and Dr. H. Spencer (Departments of Pathology and Neurology, St. Thomas' Hospital).

The case histories of two fatal examples of leuco-encephalitis were displayed, together with representative strips from their EEGs.

Case I.—Female. Onset aged 10 years.

A gradual deterioration in her behaviour took place over six months. She became unteachable at school, used the wrong tools at table and misdressed herself. The diagnosis of hysterical rebellion against authority had been considered. Several fits were followed by more obvious dementia.

The only abnormal findings were:

(1) EEG.

(2) Paretic Lange in otherwise normal C.S.F.

On these the diagnosis was made, and confirmed by cerebral biopsy. Death occurred about one year after onset.

Case II.—Female. Onset aged 5 years.

Presented with *petit mal*. The diagnosis was made on the EEG appearance, after experience with Case I, before there was any clinical suspicion. C.S.F.—Lange was paretic; no other abnormality.

The child became gradually demented and died after nine months.

EEGs.—Typical tracing is diagnostic. Serial tracings are often necessary before pathognomonic complexes appear. The fully developed picture is of periodic bursts of high voltage slow activity in all leads of highly characteristic pattern occurring at regular intervals. The exact interval varies from case to case but is often constant in a given case. The EEG bursts may be correlated clinically with momentary lapses of consciousness. This EEG cannot be confused with the spike and wave complex of *petit mal*.

Pathology.—Sections of brain were shown demonstrating evidence of a virus encephalitis, perivascular cuffing with lymphocytes and diffuse destruction of nerve cells, mainly confined to the cerebral cortex. This change disappeared below the level of the pons being maximal in frontal and parietal cortex. The distinctive feature of this form of encephalitis is the presence of intra-nuclear inclusion bodies best demonstrated by phloxine tartrazine staining. Very occasionally the inclusion bodies are found in the cytoplasm of affected cells. Demyelination could not be demonstrated in the white matter.

Growth of the Fœtal Skull.—Dr. E. H. R. Ford (Department of Anatomy, St. Thomas' Hospital Medical School).

Measurements on dissected fœtal heads show that between 10 and 40 weeks the anterior (perchordal) part of the cranial base and the brain grow faster than the parachordal part of the base, producing flattening of the spheno-ethmoidal and foramino-basal angles, and increasing occipital protuberance. The chondrocranium and foramina for cranial nerves move relatively nearer to the midline. The face becomes relatively broader but the degree of prognathism remains constant. Mandibular growth is retarded between 12 and 20 weeks whilst the secondary condylar cartilage is developing.

REFERENCE

Ford, E. H. R. (1956) *J. Anat., Lond.*, **90**, 63.

The Measurement of Neonatal Blood Pressure.—Dr. W. W. Holland and Dr. I. M. Young (Department for Diseases of Children, and Obstetrics and Gynæcology and the Sherrington School of Physiology, St. Thomas' Hospital).

The systolic blood pressure was measured using the occlusion technique with a 2·5 cm. wide cuff and palpation of the brachial artery in the ante-cubital fossa. Measurements were made within one hour of birth and the infants were followed up to the age of 6 months.

The mean systolic blood pressure at birth was found to be 70 mm.Hg in normal infants, delivered normally. At 6 months the mean systolic blood pressure in these infants was found to be 95 mm.Hg.

Infants suffering from "white asphyxia" at birth, had a systolic blood pressure significantly lower at birth, which remained lower than normal babies until the tenth day. Similarly

babies born by Cæsarean section, for whatever indication, had significantly lower systolic blood pressures at birth than normals. Babies born of mothers suffering from toxæmia of pregnancy did not have systolic blood pressures higher than normal babies.

Further observations and details are being published.

Acute Osteitis.—Dr. J. F. COLLINS for Dr. B. D. R. WILSON (Children's Department, St. Thomas' Hospital).

A chart was shown demonstrating some clinical features, the mode of therapy and the outcome in each of 15 cases of acute osteitis, which had been treated in the medical wards during the five years up to 1955.

The following were the more important points arising out of this study:

(*a*) In acute febrile illnesses in childhood the need for a lower threshold for the diagnosis of acute osteitis is evident from the fact that in no case had it been considered before admission to hospital or until localizing signs made it obvious four to eight days after the onset.

(*b*) Prior to local swelling the combination of the following four clinical features was very frequent, and should therefore suggest the diagnosis at an early stage: complete anorexia, temperature in excess of 102° F., nocturnal delirium and pain sufficient to interfere with sleep. Below the age of 3 years, however, such marked constitutional upset was not a prominent feature.

(*c*) Surgical intervention was not found necessary in any case (other than aspiration for associated septic arthritis or obvious subperiosteal abscess), but the appropriate antibiotic should be exhibited for a minimum of four weeks and for as long thereafter as local tenderness remains. Poor response or "escape" phenomenon indicates the need to review the antibiotic rather than immediate recourse to such measures as drilling of bone, &c.

REFERENCE

BREMNER, A. E., NELIGAN, G. A., and WARRICK, C. K. (1954) *Lancet*, i, 953.

Anomalous Pulmonary Venous Drainage.—Dr. A. P. C. BACON (Cardiac Department, St. Thomas' Hospital).

Anomalous venous drainage of the lungs was more common than has previously been realized, and 12 cases had recently been diagnosed at St. Thomas' Hospital by means of cardiac catherization, oximetric studies, and radiology. The abnormal venous return was most commonly to the right atrium or superior vena cava, but could be to any of the great veins in the chest or to abdominal veins.

Physiological effects were related to the extent of lung anomalously drained, major degrees of the syndrome being accompanied by markedly increased pulmonary blood flow with right ventricular hypertrophy, right bundle branch block, and congested lung fields.

Single anomalous veins were usually asymptomatic, though when one lung or more was affected, or when there was an associated atrial septal defect, symptoms arose. These included dyspnœa, hæmoptysis, palpitations, angina pectoris.

Certain surgical procedures had been devised for restoring the normal architecture, though as yet this type of cardiac surgery was in its infancy, and pre-operative knowledge of the existence and extent of anomalous pulmonary veins was of first importance.

REFERENCE

HICKIE, J. B., GIMLETTE, T. M. D., and BACON, A. P. C. (1955) *Brit. Heart J.*, **18**, 365.

Spread of *Staph. pyogenes* in Maternity Departments.—Dr. MARY BARBER (Department of Bacteriology, St. Thomas' Hospital Medical School).

In studying an outbreak of severe staphylococcal infection in a Maternity Unit in 1949, Barber *et al.* isolated a single strain of *Staph. pyogenes* phage-type 52A resistant to penicillin from nearly all infective processes. The same organism was also isolated from the conjunctiva of many healthy babies and from the nasopharynx of about 50% of all nurses who had been in the hospital for three months or longer. It seemed clear, therefore, that a single strain of *Staph. pyogenes* was spreading round the department. The incidence of infection remained high, in spite of increased measures of aseptic control, until the hospital was temporarily closed and the wards cleaned.

Further studies (*cf.* Barber *et al.*, 1953; Barber and Burston, 1955) have shown that pathogenic strains of staphylococci appear to spread round a maternity department to the same extent, even when the sepsis rate is very low. Thus in a "clean" maternity department in 1953 it was found that 65% of all babies went home with penicillin-resistant

Staph. pyogenes in the nasopharynx, and in 1955 in the same department the figure was 89%. The nasal carriage rate of penicillin-resistant *Staph. pyogenes* among the nurses in the department was 45% in 1952 and 61% in 1955. Just under half the strains isolated from both babies and nurses were phage-type 52A.

Bacteriological studies, therefore, reveal little difference in the spread of *Staph. pyogenes* in a department with an outbreak of serious infective processes and in a department free from major sepsis. Presumably in the presence of sepsis the virulence of staphylococci is increased and it seems probable that strains carried for long periods in the nasopharynx become relatively resistant, although it is difficult to demonstrate this by laboratory tests. As a practical measure, however, it is probably much more important to isolate all people with infective processes whether mothers, babies or nurses, than to be too greatly concerned with nasal carriers.

REFERENCES

BARBER, M., and BURSTON, J. (1955) *Lancet*, ii, 578.
——, HAYHOE, F. G. J., and WHITEHEAD, J. E. M. (1949) *Lancet*, ii, 1120.
——, WILSON, B. D. R., RIPPON, J. E., and WILLIAMS, R. E. O. (1953) *J. Obstet. Gynæc., Brit. Emp.*, **60**, 476.

An Aid to the Diagnosis of Atrial Septal Defect.—Dr. T. D. GIMLETTE and Dr. G. de J. LEE.

A demonstration was given of a simple test for atrial septal defect. The principle makes use of the similar pressures existing in the right and left atrium at rest. If a sudden rise in right atrial pressure could be produced without a corresponding change in left atrial pressure, then a temporary right to left shunt would occur if an atrial septal defect existed.

A convenient method for producing sudden changes in right atrial filling pressure is by means of Valsalva's manœuvre. The patient's arterial oxygen saturation is continuously recorded by an ear oximeter. After a short control period, the patient blows against a mercury column and maintains a pressure of 50 mm.Hg for 10–12 seconds. This has the effect of raising the intrathoracic pressure and impairing venous return to the right atrium. The arterial oxygen saturation usually rises slightly during this period if an atrial septal defect exists. On release of Valsalva's manœuvre, normal right atrial filling is resumed and the right atrial pressure rises steeply, with the results that a temporary right to left shunt through the atrial defect is produced. This results in a transient fall in arterial oxygen saturation below the resting level.

28 cases of atrial septal defect, proved by cardiac catherization, have been studied in this way. All gave a positive response to the test. The patients' ages ranged from 4–31 years. Small atrial septal defects may give a negative response unless the patient is exercised prior to the test. Cases with ventricular septal defect show no change in arterial saturation as a result of the test. Preliminary observations in patients with Fallot's tetralogy appear to show different arterial oxygen saturation changes to those obtained in cases of atrial septal defect.

The following demonstrations were also given:

Clinical Photographs.—Dr. F. C. V. BRIGHTMAN.

X-rays.—Dr. J. SUTCLIFFE.

A number of clinical cases were shown.

Problems Arising in the Management of Staphylococcal Pneumonia in Infants and Children

By B. D. R. WILSON, M.B., M.R.C.P., D.C.H.

A NUMBER of slides of X-rays were shown, illustrating the problems associated with staphylococcal lung infection. Although it was not possible to distinguish radiologically between primary and secondary pneumonias (Gibson and Belcher, 1951) this did not affect their management.

Empyemata were first considered and most conveniently treated by parenteral penicillin, aspiration and penicillin replacement. Unfortunately, due to the frequency of infection with resistant organisms, especially during the early months of life, penicillin could no longer be regarded as the antibiotic of choice. The tetracycline group of drugs had proved a satisfactory alternative, of which the intravenous form of Terramycin (oxy-tetracycline) had in a dosage of 50–100 mg. been successfully used to sterilize the pleural cavity, into which it was instilled after aspiration (Rackow, 1953). Pleural loculations were another feature

of these empyemata, and their treatment consisted of multiple aspirations and antibiotic replacement at different sites. Intercostal drainage in such cases was contra-indicated.

Spontaneous pneumothorax *per se* required no treatment other than that of the underlying infection. By contrast, tension pneumo- or pyopneumo-thorax constituted an acute medical emergency. Emergency treatment consisted of aspirating air through a needle thrust into the pleural cavity, after which the problem was one of sucking air out of the pleural cavity faster than it entered. A simple and effective system consisted of the rubber cap from a transfusion bottle, through which a large bore needle or trocar and canula had been thrust into the pleural space. One of two pieces of polythene tubing of equal length is inserted so that its distal end is through the needle or canula, which is then withdrawn. The second piece of polythene is used to measure the length within the chest. Finally the rubber cap is strapped to the chest wall and the system connected to an electrical suction pump. If the lung can be kept expanded for forty-eight hours, it sticks and causes no further trouble. Residual shift of the mediastinum to the side of the lesion had caused anxiety as to whether pleural thickening might permanently interfere with re-expansion and function of the lung, which raised the question of decortication during the acute phase. Expectant treatment had proved amply justified, although in one case two years had elapsed before the mediastinum finally became central.

When referring to lung "cysts" the term was used to cover the cystic phase characteristic of staphylococcal pneumonia without implying that they were true cysts. The typical "soap bubble" or "egg-shell" cysts were shown in some cases to disappear as rapidly as they came, while in others they persisted for several months or longer. Persistent cysts, provided they gave rise to no symptoms, required no treatment but where they were subject to recurrent attacks of inflammation or caused symptoms from air under tension, surgical excision had to be undertaken.

Of the complications during the acute phase, meteorism proved an additional embarrassment to respiration in infants, which the passage of stomach and flatus tubes did little to relieve. The importance of the correction of rapidly developing anæmia, which may be easily overlooked, was stressed. Bronchiectasis was one of the late complications of severe staphylococcal pneumonia.

Difficulties in diagnosis could arise from confusion between diaphragmatic hernia and pyopneumothorax, although X-rays in different postures could often settle the point. It could be extremely difficult to differentiate loculated pyopneumothoraces from cysts containing fluid in the lung itself. Needling of the latter in error could result in unpleasant complications such as pneumothorax and surgical emphysema.

In conclusion it was shown that although staphylococcal pneumonia was not a common condition, the correct treatment of the primary infection and its complications produced gratifying results.

REFERENCES

GIBSON, M. O. J., and BELCHER, J. R. (1951) *Quart. J. Med.*, N.S. **20**, 43.
RACKOW, F. (1953) *Brit. med. J.*, i, 11.

[*March* 23, 1956]

"Any Questions"

A PANEL composed of Dr. G. O. BARBER, Dr. H. V. HUBBLE, Professor R. S. ILLINGWORTH and Dr. WILFRED SHELDON had a spontaneous discussion on questions regarding pædiatric problems, put forward by Members. The subjects of the questions were:

A Definition of Epilepsy and the Treatment of this Condition.

The Treatment of Recurrent Abdominal Pain in the Absence of an Organic Cause.

The Treatment of Chronic Constipation in the Schoolchild.

The Management of Asthma.

The Use of BCG Vaccination.

The Reaction of the Urine in Nocturnal Enuresis.

BOOKS RECEIVED FOR REVIEW

Adriani (J.). Techniques and procedures of anesthesia. 2nd edit. pp. xiv + 568. Oxford: Blackwell. 66s. 0d. 1956.

Bencard. Manual of Allergy. pp. 95. London: C. L. Bencard Ltd., Allergy Division. 1956.

Biot (R.), and Galimard (P.). Medical guide to vocations. pp. xx + 303. London: Burns & Oates. 18s. 0d. 1955.

Cameron (G. R.). New pathways in cellular pathology. pp. vii + 90. London: Arnold. 16s. 0d. 1956.

Garland (G. W.) and Quixley (J. M. E.) Obstretrics and gynæcology for nurses. pp. xii + 188. London: English University Press. 10s. 6d. 1956.

Griffiths (D. Ll.), Seddon (H. J.), and Roaf (R.). Pott's paraplegia. pp. xiv + 129. Oxford University Press. London: Cumberlege. 50s. 0d. 1956.

Himsworth (Sir Harold), and Delafresnaye (J. F.), eds. The support of medical research. A symposium organized by the Council for International Organizations of Medical Sciences. pp. xi + 170. Oxford: Blackwell. 17s. 6d. 1956.

Le Vay (D.). The life of Hugh Owen Thomas. pp. vii + 135. Edinburgh and London: Livingstone. 25s. 0d. 1956.

Rackemann (F. M.). The inquisitive physician: the life and times of George Richards Minot, A.B., M.D., D.Sc. pp. xi + 288. Harvard University Press. London: Cumberlege. 40s. 0d. 1956.

Rosenblatt (M. B.), and Lisa (J. R.). Cancer of the lung: pathology, diagnosis and treatment. pp. xiii + 330. New York: Oxford University Press. London: Cumberlege. £6 0s. 0d. 1956. (*Amended notice.*)

Smith (H. W.). Principles of renal physiology. pp. x + 237. Oxford University Press. London: Cumberlege. 40s. 0d. 1956.

Walton (J. N.). Subarachnoid hæmorrhage. pp. xv + 350. Edinburgh and London: Livingstone. 30s. 0d. 1956.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

John (H. J.). Diabetes: a concise presentation. pp. 300. London: Kimpton. 17s. 0d. 1946.

Jones (Ernest). Sigmund Freud: life and work. Vols. **1** and **2**. London: Hogarth Press. Vol. **1**, 27s. 6d.; Vol. **2**, 30s. 0d. 1953–1955.

Jonkhoff (H. B.). Bepaling van de telefoon-karakteristiek aan het oor zelf. pp. 62. Amsterdam: Holland N.V. 1956.

Joyeux (C.). Précis de médecine coloniale. 3rd edit. pp. 1058. Paris: Masson. Fr. 470. 1944.

Kaiser (M.). Pocken und Pockenschutzimpfung. pp. 207. Vienna: Springer. 1949.

Kopaczewski (W.). Cl. Bernard et la physiologie. pp. 81. Rabat: "Maroc-Matin." 1945.

Leveuf (J.), and Bertrand (P.). Luxations et subluxations congénitales de la hanche. pp. 279. Paris: Doin. 1946.

Lillie (R. D.). Histopathologic technic. pp. 300. Philadelphia and Toronto: Blakiston. 28s. 6d. 1948.

Low (R. C.). Carbonic-acid snow as a therapeutic agent in the treatment of diseases of the skin. pp. 117. Edinburgh and London: Wm. Green. 1911.

Ludwig (C.). De rivibus physicis secretionem urinae adjuvantibus. pp. 23. Marburg. 1842. (Photocopy.)

Manson-Bahr (Sir Philip). History of the School of Tropical Medicine in London (1899–1949). pp. 329. London: Lewis. £2 10s. 0d. 1956.

Marriott (H. L.). Water and salt depletion. pp. 80. Oxford: Blackwell. 8s. 6d. 1950.

Mellor (J. W.), 1873–1938. Mellor's modern inorganic chemistry. Revised and edited by G. D. Parkes in collaboration with J. W. Mellor. 9th edit. pp. 915. London: Longmans. 14s. 0d. 1939 (reprint 1943).

Montpellier (J.-M.). Autour du problème du cancer. I. pp. 337. Alger: Ferraris. 1944.

Peters (J. P.), and Van Slyke (D. D.). Quantitative clinical chemistry. Vol. **1**. 2nd edit. pp. 1041. London: Baillière. 38s. 6d. 1946.

Polonovski (M.), ed. Exposés annuels de biochimie médicale. 4th ser. pp. 284. Paris: Masson. Fr. 160. 1944.

Potter (E. L.). Pathology of fetus and newborn. pp. 574. Chicago: Year Book Publishers. £7 10s. 0d. 1952.

Roemheld (L.). Die Bacillenruhr. pp. 125. Stuttgart: Thieme. 1949.

Rome. Istituto di Medicina Sociale. Atti del II Convegno Nazionale su "L'azione della medicina sociale per la rinascita del delta Padano," Ferrara 11–12–13 Giugno 1955. pp. 292. Rome. 2,000 lire. 1956.

Section of Odontology

President—Professor H. H. STONES, M.D., M.D.S., F.D.S., R.C.S.

[*February* 27, 1956]

Muco-epidermoid Odontogenic Cysts of the Jaws with Special Reference to those in the Mandible

By J. J. HODSON, Ph.D., B.D.S., L.D.S. R.C.S.

ODONTOGENIC cysts are usually lined by stratified squamous epithelium. Occasionally cysts in the maxilla may contain in places a respiratory epithelium with a few goblet cells which is said to arise from the antrum or nose. Stafne and Millhon (1945) found one such case in 88 epidermoid cysts of the jaws. I have found 4 in 54 maxillary dental cysts. There is little information in the literature regarding the presence and nature of mucous cells in odontogenic cysts, and no mention of them in cysts of the mandible. Sonesson (1950), Stones (1954) and others note their occasional presence but give no details. Linell (1948) found 4 cases (6%) out of 70 which showed goblet cells in the squamous epithelium. He illustrates one but does not say whether they were present in mandibular or maxillary cysts, or both.

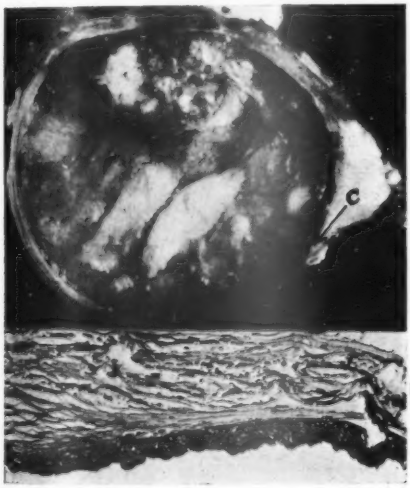


FIG. 1.—A, Cut surface of enucleated residual cyst from premolar area of mandible of male age 32. Two years' history. Contents, fat, cholesterol, blood, &c. Cyst wall (C), fibrous tissue with scattered patches of chronic inflammatory cells, a few epithelial clumps, some with mucous changes—cyst lining, stratified squamous epithelium, half of which was replaced by mucous cells. B, Goblet cells in cyst lining backed by one or two layers of flattened epithelial cells. Hæmatoxylin and mucicarmine. × 89.

In 1949 a residual cyst of the mandible was received for routine histological report and sections showed that a large part of the stratified squamous epithelial lining contained goblet and other shaped mucous cells (Fig. 1). Since then, 89 odontogenic cysts have been examined and out of 53 maxillary cysts 12 contained mucous cells (22%) and out of 36 mandibular cysts 8 contained mucous cells (22%). Those cysts containing mucous cells may be termed muco-epidermoid cysts. Table I shows an analysis of the cysts examined.

TABLE I

Site	Radicular	Residual	Eruption	Dentigerous	Lateral	Total	
EPIDERMOID CYSTS							
Maxilla	18	13	6	4	0	41	69
Mandible	6	15	1	2	4	28	
MUCO-EPIDERMOID CYSTS							
Maxilla	3	7	0	2	0	12	20
Mandible	2	6	0	0	0	8	

Total Cysts 89. Muco-epidermoid 22%.

Maxillary cysts 53—Muco-epidermoid 22%. Mandibular cysts 36—Muco-epidermoid 22%.

The 53 cysts in the maxilla include 2 radicular cysts and 1 residual cyst containing portions of respiratory epithelium (one recent one not included). The number of mucous cells varied from a few to many, sometimes comprising half or more of the luminal cells. Identification was based on morphology, routine metachromasia, and staining with mucicarmine and the periodic-acid Schiff reagent. It may be pointed out that more than one kind of mucin may be present and eosinophilic mucins may occur within cysts and cells. In epithelial pearls the latter may be mistaken for keratin (Fig. 5B). The age range of the muco-epidermoid cysts was 28–79 years, which does not differ from that of the usual epidermoid cysts.

FIG. 2.—Bi-loculated residual cyst in mandible—male age 59—history three years. No solid contents —moderate acute and chronic inflammatory cell infiltration.

The finding of a similar percentage of muco-epidermoid cysts in the mandible to those in the maxilla (Figs. 1–5), indicates that proximity to the antrum or nose does not explain their presence. Detailed microscopic study shows that except for the respiratory goblet cells, the mucous cells arise by metaplasia of squamous, and possibly intermediate cells. In many cases, adjacent cells with dense granular cytoplasm are seen and are suggestive of pre-mucous changes. The mucous cells may be found on the luminal surface of the cyst (Figs. 1B and 3A), also deep within the squamous epithelium, sometimes forming intra-epithelial mucous

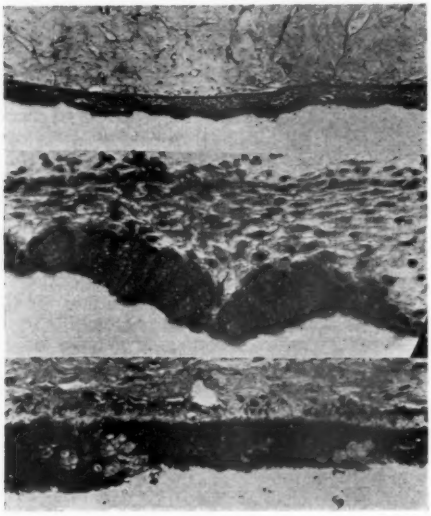


FIG. 3.—Areas from the wall of cyst in Fig. 2. A, Low power showing dense fibrous tissue and stratified squamous epithelial lining with extensive replacement of the surface layer by goblet cells. Hæmatoxylin and periodic-acid Schiff reagent. × 58. B, High power showing goblet cells. Hæmatoxylin and mucicarmine. × 244. C, Showing intra-epithelial mucous gland-like formations Hæmatoxylin and eosin. × 112.

gland-like formations (Fig. 3c) and sometimes forming mucous microcysts (Fig. 4B). Their form as goblet-shaped cells (Fig. 3B) or flattened squames depends on the degree of intracystic pressure. They may also be found in columns, clumps and epithelial pearl-like nests of hyperplastic epithelium within the fibrous tissue of the cyst wall (Fig. 5B). They are present in inflamed, desquamating epithelium, in stabilized uninflamed cysts with sclerotic walls and also the pseudo-adamantinomatous spongiosis commonly seen in squamous epithelium of dental cysts.

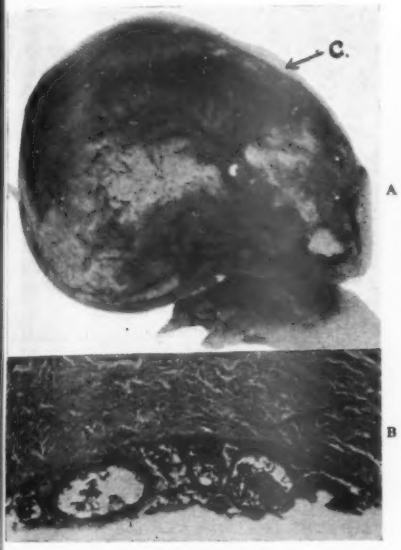


FIG. 4.—A, Cut surface of residual cyst in premolar area of maxilla—male age 49. History six months. Contents, fat, cholesterol, calcium deposits, mucin, &c. Fibrous wall (C) showed no inflammatory cellular infiltration. B, Showing microcysts lined by goblet cells in stratified squamous epithelial lining. Hæmatoxylin and mucicarmine. × 148.

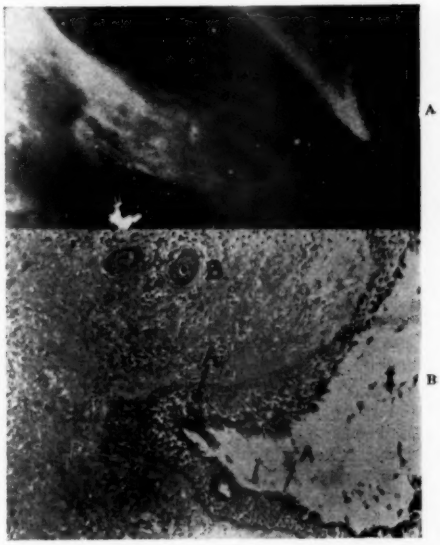


FIG. 5.—A, Residual cyst in mandible with root fragment—female age 54, history of five years. No loose contents. B, Section of cyst wall showing mucous cells on luminal surface and deeper within stratified squamous epithelium (A)—also mucous changes in epithelial nests (B). Cyst wall showed moderate inflammatory cell infiltration. Hæmatoxylin and mucicarmine. × 69.

What is the significance of the presence of these metaplastic mucous cells in jaw cysts? I am not convinced that they are primarily degenerative in nature, although many of them appear to succumb to their own secretion or desquamate into the cyst lumen. Stewart *et al.* (1945) have stated that in salivary tumours, mucous cells once formed, have considerable powers of proliferation. It may be that their presence reflects the glandular potentialities of the oral epithelium. Their formation from squamous cells, however, does not add to this possibility, and I would regard the metaplasia as environmental in origin, i.e. an interference with cell metabolism. Our interest in the muco-epidermoid cysts lies in their similarity to the cystic areas and epidermoid proliferation in muco-epidermoid salivary tumours and muco-epidermoid features of adamantinomas (*Brit. J. Plastic Surg.* In press). We are also interested in the question whether these cysts show any different clinical behaviour to the ordinary epidermoid cysts. This is a long-term investigation which depends a great deal on the willingness of patients to return for further examination.

I am indebted to Professor G. L. Roberts, Mr. R. Rastall, Mr. T. Battersby and Mr. R. C. W. Dinsdale for the clinical material, and to Mr. M. Rudland for technical assistance.

REFERENCES

LINELL, F. (1948) *Acta path. microbiol. scand.*, **25**, 801.
SONESSON, A. (1950) *Acta radiol., Stockh.*, Suppl. 81.
STAFNE, E. C., and MILLHON, J. A. (1945) *J. oral Surg.*, **3**, 101.
STEWART, F. W., FOOTE, F. W., and BECKER, W. F. (1945) *Ann. Surg.*, **122**, 820.
STONES, H. H. (1954) Oral and Dental Diseases. 3rd edn. Edinburgh and London.

Diseases of the Mouth Caused by the Herpes Simplex Virus

By E. D. Farmer, M.A., M.D.S., F.D.S. R.C.S.
Senior Lecturer in Parodontal Diseases
University of Liverpool

The herpes simplex virus has been shown to be responsible for lesions in many parts of the body (Kilbourne and Horsfall, 1951). The virus has a predilection for tissues arising from the embryonic ectodermal layers and particularly for those at muco-cutaneous junctions. The lesions produced are characterized by the formation of eosinophilic intra-nuclear inclusion bodies in the involved epithelial cells and the formation of vesicles within the epithelium. Specific antibodies are developed in the patient's serum during the course of the first or primary infection (Burnet and Lush, 1939), but in spite of this the virus remains in the tissues, probably for the rest of the patient's life, as a latent source of infection which may be activated by a variety of stimuli (Burnet, 1953).

The incidence of herpetic infection is very high, between 75% and 80% of the population have specific antibodies in their blood (Andrews and Carmichael, 1930; Hayward, 1950) indicating that they have been infected at some time in their lives—usually before they are 6 years old (Rogers, Coriell, Blank and Scott, 1949).

According to Burnet and Williams (1939), a common manifestation in children of the primary infection with the herpes simplex virus is an acute stomatitis. On recovery the virus survives in the tissues producing occasional or recurrent lesions in the form of herpes labialis or common "cold sores".

Several workers have investigated this condition in children and among these Black in 1942 confirmed the association between the acute stomatitis and herpes labialis by inoculating the gum of a 1-year-old child with the contents of a herpetic vesicle from the lip of an adult and produced the typical symptoms of an acute herpetic stomatitis.

Although the condition is more common in children, Cahn (1950) considers that it is not rare in young adults and a number of cases have been reported in the literature (Youmans, 1932; Long, 1933; Ziskin and Holden, 1943; Rogers *et al.*, 1949; Kilbourne and Horsfall, 1951).

The present paper is concerned mainly with acute herpetic stomatitis and its sequelæ. A brief summary of the clinical condition and its treatment in children and adults will be followed by a description of the laboratory diagnosis of the condition and a discussion of the findings in the cases examined.

Clinical Findings

54 patients with an acute stomatitis have been examined during the past three years and diagnosed clinically as acute herpetic stomatitis. 36 were between the ages of 16 and 46 and 16 were under 10 years of age. The incidence was fairly evenly distributed between the sexes and seemed to be more prevalent between the months of September and May, with December as the peak month. 16 cases had a history of contact with recent "cold sores", or with mouth ulcers. 6 had a previous history of "cold sores" and 1 of mouth ulcers.

The clinical findings in children have been well described by Black (1938 and 1942) and are similar to those found in adults, except that in the child the condition is usually more severe with temperatures up to 105° F. A proportionately higher number (5 out of 16) presented with lesions on the face as well as in the mouth. According to Black (1942) the symptoms subside on the sixth day of fever in the untreated case and the condition has cleared by the fourteenth day. In one of the cases from which a virus was isolated from the mouth on the fourth day of illness, a group of typical herpetic vesicles appeared eight days later on the back of the left hand, a place frequently sucked by the child. Similar viruses were isolated from the lesions in both sites.

In the adult, the first symptoms may include soreness or pain in the mouth and throat, bleeding, swollen and painful gums, discomfort on swallowing, enlarged and tender submaxillary glands and general malaise. Two or three days after the onset of symptoms small rounded vesicles appear anywhere on the oral mucosa, tongue and lips. The vesicles may be well filled (Fig. 1) but more usually present with a slightly raised crinkly greyish-white covering which is easily removed. The vesicles rapidly break down to form small shallow saucer-like ulcers with reddened margins. They may be discrete or confluent and when confluent the resulting ulcer is irregular in outline. Similar lesions appear on the tongue, palate, and pharyngeal mucosa. As on the lips and buccal mucosa these are usually larger than on the gingivæ and attached mucosa. The lips are usually dry and scaly and often show large crusted lesions (Fig. 1). Lesions on the white skin of the face were seen only in two of the patients over 16 years of age.

FIG. 1.—Showing two well-formed vesicles and a large crusted lesion on the lower lip. The upper lip is dry and scaly in appearance.

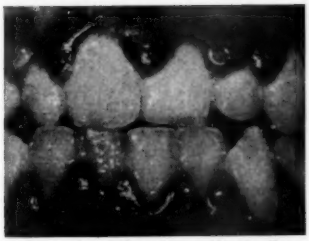


FIG. 2.—Discrete and confluent lesions involving the upper gingivæ. The lower gingivæ are swollen and reddened but not ulcerated.

FIG. 3.—A small vesicle on the labial surface of the central papilla. This lesion came five weeks after the acute stomatitis seen in Fig. 2. The rest of the mouth was unaffected.

In some cases the gingivæ are unaffected, but more frequently they are painful, enlarged, reddened and bleed easily. Discrete or confluent vesicles or ulcers may be present (Fig. 2). While the tips of the papillæ were occasionally included these were never the only site involved by the lesions.

The treatment included gentle cleaning of the mouth and the vigorous use of a mouthwash containing 1% Aureomycin in 10% glycerin every four hours for two to three days. In very young children the mouth was swabbed every four hours with a similar solution containing 3% Aureomycin. To prevent the formation of a furred tongue, the patient was told to brush the dorsum each time after using the mouthwash. Owing to the frequency with which yeasts developed during this treatment the patients were instructed to use an additional mouthwash contain 0·5% sodium caprylate, one hour after the Aureomycin. In most cases a period of between two and ten days had elapsed between the onset of symptoms and the start of treatment. There was usually a marked improvement in the condition within twenty-four hours. The ulcers frequently remained for some time after the symptoms had disappeared but these eventually healed without scar formation. Those cases with swollen gingivæ recovered more slowly than those without, but usually the patients were ready for discharge seven to twelve days after the treatment had been started.

13 cases had received previous treatment with either local or systemic penicillin but none had shown any marked response to this treatment. One case had been treated unsuccessfully with penicillin troches for twenty-five days. Gentian violet and hydrogen peroxide were also used but they were less effective than Aureomycin. Systemic Aureomycin showed no advantages over its local application.

Recurrences.—31 patients were examined at intervals of between six months and three years after the acute infection. 21 gave a history of what was presumed to be a recurrence in one form or another. 4 patients reported having had lesions confined to the lip, 7 with vesicles or ulcers in the mouth and on the lips, while the remaining 10 had noticed vesicles or ulcers only in the mouth. In some cases frequent recurrences had been experienced, but in the majority of patients these had occurred on only three or four occasions, the number of recurrences usually becoming less with the passage of time. Most of the patients with recurrences noticed that only one or two vesicles or ulcers appeared on each occasion but in one case, a child aged 3, a generalized stomatitis was experienced nine months after the first attack. None of these patients with a history of recurrence had experienced ulcers in the mouth, or "cold sores", prior to the onset of the acute condition.

Only 3 cases were seen at the time of the recurrence. The lesions (Fig. 3) were similar

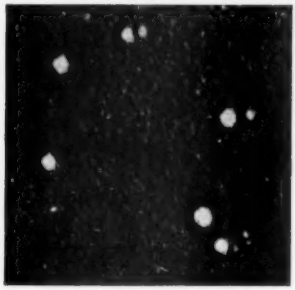


FIG. 4.—Electron microscope pictures of shadow-cast spherical virus particles. The large particles are about 100–150 mμ while the smaller particles are about 50 mμ in diameter. The line represents 1μ. × 5,700.

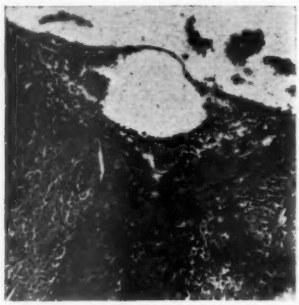
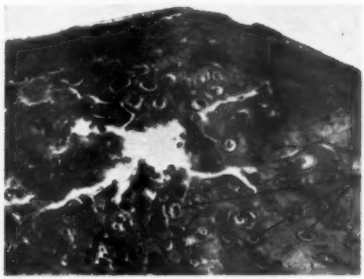


FIG. 5.—Small intra-epithelial vesicle found on the fifth day of illness. Most of the contents of the vesicle have been lost. A few lymphocytes remain enclosed by the thin vesicle wall. × 85.



Nuclei with inclusion bodies and showing margination of chromatin

FIG. 6.—Intra-nuclear inclusion bodies seen in the epithelial cells at the periphery of a lesion. The "margination" of the chromatin of the nucleus is clearly seen. × 208.

to the vesicles found in the primary infection, but the pain was localized to the lesion, no glands were involved and the patient felt well. In 2 of the cases an attempt to isolate a virus was unsuccessful. Histological examination of the third showed the presence of typical intra-nuclear inclusion bodies within the involved epithelial cells (Fig. 9).

LABORATORY PROCEDURE

Methods.—Routine bacteriological examination was carried out on all cases during the period of observation. The antibiotic sensitivity of the bacteria using Aureomycin, Terramycin, chloramphenicol, streptomycin, erythromycin, penicillin and bacitracin was also tested.

Virus isolation was achieved by drying the mucosa, removing the vesicle cap where this was present, and scraping the base of the lesion with a sterile large spoon excavator and immediately mixing the scrapings into 0·5 ml. of phosphate-buffered broth containing 100 units of penicillin and 100 mg. streptomycin per ml. This suspension was kept at + 4° C. and, as soon as possible, 0·2 ml. was inoculated on to the chorio-allantoic membrane (C.A.M.) of each of four twelve-day-old fertile hens' eggs. After incubation for forty-eight to seventy-two hours the membranes were harvested and examined for pock formation. The membranes were ground up and the virus submitted to further passages and stored at − 80° C.

Virus identification was attempted by macroscopical and microscopical examination of the pocks; the C.A.M. neutralization of a standardized washed suspension of the egg-adapted virus (usually after the tenth passage) by known herpetic anti-serum; and by the electron microscope examination of a washed suspension of the virus.

Blood examination was carried out on about 20 ml. of blood taken by venipuncture. Routine blood examination was done on 2·5 ml. and the antibody titre of the serum was

found by using the constant-antigen C.A.M. neutralization technique with one of the viruses isolated and also with a known herpes simplex virus (McCarthy).

Biopsies were taken with a minimum of trauma and fixed in Zenker-formol fixative. Serial sections were stained with routine hæmatoxylin and eosin. Specific stains were also used but showed no advantages.

Results.—Bacteriological findings were not constant except that in all cases on first testing the bacteria present were sensitive to Aureomycin, chloramphenicol and Terramycin. Alpha-hæmolytic streptococci were present in almost all cases and in 8 cases Lancefield group A beta-hæmolytic streptococci were found. During treatment with the Aureomycin about half the number of cases developed an almost pure growth of yeasts which were resistant to all the antibiotics used. This was found to be controlled by the additional mouth-wash of 0·5% sodium caprylate, in the 12 cases where this was used. After the antibiotic treatment had been completed the normal commensal bacterial growth soon developed.

A virus was isolated at the first examination from 21 of the 36 cases where this was attempted. The duration of the illness before the successful attempts were made was between three and ten days. Some of the attempts that failed also came within this period. No attempt was made to see if a virus was still present after the treatment had been started.

It is probable that the viruses isolated from each of the cases were similar to each other and that they were the herpes simplex virus.

Macroscopically the pocks produced on the C.A.M. looked similar to those produced by the known herpes simplex virus and microscopical examination revealed typical eosinophilic intra-nuclear inclusion bodies within the proliferating ectodermal cells.

Standardized suspensions of the washed viruses were similarly, but not identically, affected in neutralization tests using known herpes simplex anti-serum and by high titre sera obtained from patients recovering from the acute stomatitis.

Electron microscope examination of washed suspensions of the known herpes simplex virus (McCarthy) and five of the viruses isolated in this work revealed no obvious morphological difference between the viruses examined (Fig. 4). The virus particles were apparently spherical and between 100 to 150 mμ in diameter. Some smaller particles of about 50 mμ were also found. These findings seemed to agree with those of Coriell *et al.* (1950), and Morgan *et al.* (1954).

Sera were taken from 13 patients over 16 years of age, in the early stages of the acute condition and again during convalescence or later. The neutralization tests carried out on these sera demonstrated that all cases, excepting one, showed a marked increase in specific antibody titre during the course of the disease, indicating that in these 12 cases the infection was a primary herpetic infection. The exception, a patient aged 46 with a previous history of "cold sores", showed similar high antibody titres both in the sera taken on the sixth day of illness and again twenty-four days later.

It was found that in the primary infection antibodies start to be detectable between the fifth and seventh days of illness and the titre continues to increase even as late as between the fifteenth and twenty-fifth days of illness. The 3 cases where sera were obtained after periods of two and a half to four and a half months showed the largest differences in titre between the early and late sera.

Confirmation of the herpetic origin of the infection by both virus isolation and serological examination was achieved with 7 patients.

The blood picture in all the 13 cases tested was within normal limits except for a slight increase in neutrophil polymorphonuclear leucocytes. One case showed a few primitive mononuclear cells which resembled those often found in the blood of patients with glandular fever. The Paul-Bunnell test was not significantly positive in this and 3 other cases.

Biopsy findings.—Biopsies were taken from 9 patients during the acute condition. A further biopsy was taken from one of these patients and included a single vesicle which appeared five weeks after the primary infection. The herpetic origin of the primary condition had been confirmed by both virus isolation and serological examination in 4 cases and by serological examination only in a further 4 cases.

Small intra-epithelial vesicles (Fig. 5), but no inclusion bodies, were found in biopsy specimens taken from 2 cases, one on the fifth and the other on the twenty-fifth day of illness. Biopsies taken from 5 patients between the fourth and seventh days showed typical inclusion bodies in some of the epithelial cells adjacent to, or involved in, vesicle or early ulcer formation (Fig. 6). Another, taken on the sixth day, showed what appeared to be non-specific ulcer formation with no inclusion bodies, while that taken on the twelfth day showed a healing lesion with no inclusion bodies present.

Within the mouth the mature vesicle was found to be covered by one or two layers of flattened epithelium. The vesicles, when intact, appeared to be filled with a weakly

eosinophilic mass which was slightly granular or fibrinous in character (Fig. 8). Some inflammatory cells were sometimes present.

The cells in which inclusion bodies were found showed a "margination" of the chromatin, with an amorphous or slightly granular eosinophilic mass within the nucleus (Figs. 6 and 9). In most of the specimens where inclusion bodies were found, large "multinucleated" cells with little or no cytoplasm were also found within the lesion (Fig. 7). These cells are similar to those said to be found in scrapings taken from the vesicles or ulcers (Glickman, 1953), but attempts to find these cells in smears from 10 cases were not successful.

The biopsy including a lesion recurring five weeks after the original infection (Fig. 3) showed a small vesicle (Fig. 8) with some typical inclusion bodies in the involved epithelial cells (Fig. 9). This biopsy was taken one day after the lesion had developed. Similar inclusion bodies were found in the lesions of the primary condition.

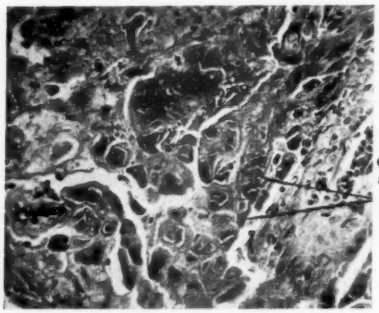


FIG. 7.—Section showing groups of nuclei with inclusion bodies giving the appearance of multi-nucleated cells reputed to be found in scrapings from these lesions. × 145.

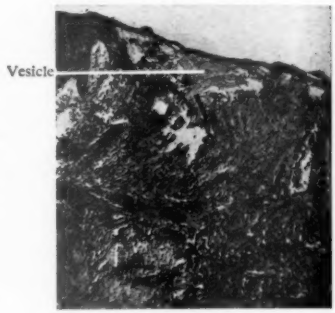


FIG. 8.—Section of vesicle seen in Fig. 3 showing the thin vesicle cap and the granular appearance of the vesicle contents. × 85.

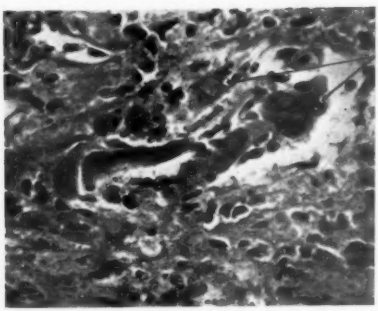


FIG. 9.—Inclusion bodies found in epithelial cells at the periphery of the vesicle seen in Fig. 8. × 212.

DISCUSSION

The diagnosis of acute herpetic stomatitis depends on four factors, namely, the clinical appearance and case history, including the history of possible contact; the isolation and identification of the herpes simplex virus; the establishment, in the primary infection, of the development of specific neutralizing antibodies in the patient's serum during the progress of the condition; and lastly the finding of intra-nuclear inclusion bodies in the early lesion. Other authorities would also include the finding of balloon cells or Tzanc cells (Glickman, 1953) in smears prepared from scrapings from the lesion.

Although each of these factors is an indication of the diagnosis of acute herpetic stomatitis, no one by itself can be regarded as a proof of the diagnosis. The case history

by itself may be misleading, and the differential diagnosis from other vesicular or ulcerative lesions of the mouth and throat, particularly herpangina caused by coxsackie virus (Huebner *et al.*, 1951), may be difficult. The isolation of the virus may be misleading, as apparently normal individuals may carry the virus in the saliva (Scott *et al.*, 1941). If the infection is not a primary infection it is not always possible to detect an increase in specific antibody titre during the course of the disease. Finally the finding of typical intra-nuclear inclusion bodies is not always a constant feature and even if found they do not constitute a proof of herpetic infection.

6 of the patients examined had a previous history of recurrent "cold sores" for several years, with no previous history of an acute stomatitis. Virus isolation from 3 cases and biopsy findings in another seem to indicate that the stomatitis seen in these cases was herpetic in origin. These findings imply that not all cases of acute herpetic stomatitis are the result of a primary infection with the herpes simplex virus.

It may be that the acute stomatitis experienced by these 6 patients was an acute recurrence of an earlier unrecognized infection, as one of the children seen in this survey reported having had an acute stomatitis nine months after the original acute stomatitis. There is, however, some evidence that there are some antigenic differences among the herpes simplex viruses (Slavin and Gavett, 1946; Jawetz *et al.*, 1955) although Burnet and Lush (1939), Hayward (1950) and Dudgeon (1950) were unable to detect any difference in the strains that they examined. If antigenic variations exist it is possible that these 6 cases were the result of an infection with a strain of the virus which was antigenically different from that causing the recurrent herpes labialis. However, it is emphasized that there is, as yet, no evidence to substantiate this statement.

It may be of interest to note that one of the patients who had a previous history of frequent recurrent "cold sores" has had no "cold sores" or ulcers over a period of two years since experiencing the acute stomatitis.

Scott *et al.* (1941) considered that the condition can be highly contagious to the susceptible population, particularly below 12 years of age. The findings in this survey indicate that adults, particularly those not previously infected, must also be regarded as susceptible. A recent case not reported in the text was a dental surgeon who developed herpes of the finger after operating on a child with herpes labialis.

Whether or not there is any relationship between the recurrent ulcers experienced after acute herpetic stomatitis and the common, and possibly non-specific, recurrent aphthous ulcers, is still very much in doubt. Kilbourne and Horsfall (1951) record one case with a history of recurrent ulcers in the mouth from which they were able to isolate a virus on three occasions. It should be noted, however, that this patient also had occasional "cold sores" and on each occasion when a virus was isolated the patient had a sore throat and general malaise. Dodd and Ruckman (1950) did not consider that the herpes simplex virus was the cause of recurrent aphthous ulcers, while Blank *et al.* (1950) were unable to detect the presence of herpetic antibodies in 5 of the 13 cases that they examined.

In preliminary work on patients with a history of recurrent aphthous ulcerations, it has been found that no virus could be isolated by C.A.M. inoculation, from the 18 cases tested. Serological examination of 4 cases showed that they had high herpetic antibody titres in spite of the fact that the patients did not suffer from "cold sores". Histological examination of very early lesions from 18 patients seems to indicate that there is more than one type of lesion. Inclusion bodies, which might be considered to resemble herpetic inclusions, have been found in only one case. It is felt that no conclusions as to the origin of recurrent aphthous ulcerations can be drawn from these findings until further work has been completed. It must be admitted, however, that the history of recurrent ulcerations following acute herpetic stomatitis seems to indicate that some cases of recurrent ulcerations of the oral mucosa may be herpetic in origin.

Summary

54 cases of clinically diagnosed acute herpetic stomatitis have been examined over a period of three years. 36 of these were between 16 and 46 years of age.

Serological evidence indicated that in 12 out of the 13 cases tested over 16 years of age the infection was a primary herpetic infection.

The herpes simplex virus was isolated from 21 out of 36 cases.

Typical eosinophilic intra-nuclear inclusion bodies were only found between the fourth and seventh days of illness.

21 out of 31 patients gave a history of occasional mild and limited recurrences of the stomatitis. Typical herpetic inclusion bodies were found on the second day in a lesion recurring five weeks after the acute stomatitis.

The relationship between herpetic stomatitis and recurrent aphthous ulcerations is discussed.

Acknowledgments.—The writer wishes to thank Professor H. H. Stones and Professor A. W. Downie for their encouragement during the course of this work. He also thanks Mr. W. Lee of the University Photographic Department for the photomicrographs, Mr. J. S. Bailie of the Photographic Department of the School of Dental Surgery for the clinical photographs and Miss M. Morgan for her assistance with the laboratory work. A grant towards the cost of this work was awarded by the Medical Research Committee of the United Liverpool Hospitals.

The electron microscope photographs were kindly taken by the Research Department of Imperial Chemical Industries, Widnes.

REFERENCES

ANDREWS, C. H., and CARMICHAEL, E. A. (1930) *Lancet*, i, 857.
BLACK, W. C. (1938) *Amer. J. Dis. Childh.*, **56**, 126.
—— (1942) *J. Pediat.*, **20**, 145.
BLANK, H., BURGOON, C. F., CORIELL, L. L., and SCOTT, T. F. MCN. (1950) *J. Amer. med. Ass.*, **142**, 125.
BURNET, F. M. (1953) *Brit. med. Bull.*, **9** (3), 173.
——, and LUSH, D. (1939) *Lancet*, i, 629.
——, and WILLIAMS, S. W. (1939) *Med. J. Aust.*, i, 637.
CAHN, L. (1950) *Oral Surg.*, **9**, 1172.
CORIELL, L. L., RAKE, G., BLANK, H., and SCOTT, T. F. MCN. (1950) *J. Bact.*, **59**, 61.
DODD, K., and RUCKMAN, I. (1950) *Pediatrics, Springfield*, **5**, 883.
DUDGEON, J. A. (1950) *J. clin. Path.*, **3**, 239.
GLICKMAN, I. (1953) Clinical Periodontology. London.
HAYWARD, M. E. (1950) *Lancet*, i, 856.
HUEBNER, R. J., COLE, R. M., BEEMAN, E. A., BELL, J. A., and PEERS, J. H. (1951) *J. Amer. med. Ass.*, **145**, 628.
JAWETZ, E., COLEMAN, V. R., and MERILL, E. R. (1955) *J. Immunol.*, **75**, 28.
KILBOURNE, E. D., and HORSFALL, F. L. (1951) *Arch. intern. Med.*, **88**, 495.
LONG, P. H. (1933) *J. clin. Invest.*, **12**, 1119.
MORGAN, C., ELLISON, S. A., ROSE, H. M., and MOORE, D. H. (1954) *J. exp. Med.*, **100**, 195.
ROGERS, A., CORIELL, L. L., BLANK, H., and SCOTT, T. F. MCN. (1949) *New Engl. J. Med.*, **241**, 330.
SCOTT, T. F. MCN., STEIGMAN, A. J., and CONVEY, J. H. (1941) *J. Amer. med. Ass.*, **117**, 999.
SLAVIN, H. B., and GAVETT, E. (1946) *Proc. Soc. exp. Biol. N.Y.*, **63**, 345.
YOUMANS, J. B. (1932) *Sth. med. J., Nashville*, **25**, 228.
ZISKIN, D. E., and HOLDEN, M. (1943) *J. Amer. dent. Ass.*, **30**, 1697.

Dr. J. A. Dudgeon (St. George's Hospital) stated that he had had similar experience in the investigation of cases of ulcerative stomatitis at the Victoria Hospital for Children and the Hospital for Sick Children, Great Ormond Street. His findings were very similar to those of Mr. Farmer. Virus could be recovered quite readily from most cases of ulcerative stomatitis either by chorio-allantoic inoculation of the chick embryo or by intracerebral inoculation of baby mice. Isolation of virus seemed to be a more certain way of establishing the diagnosis, provided cases were seen in the acute stage and had the advantage over serological tests which depended on the demonstration of a rising antibody titre in the convalescent sample of blood. He also agreed with Mr. Farmer that cytological examination of the lesions for characteristic multinucleate cells of herpes simplex was much less satisfactory in herpetic lesions of mucous surfaces than in lesions of the skin. It was possible that this was due to early maceration of the vesicles and the difficulty of obtaining epithelial tissue for examination because of the painful nature of the lesions. In a similar investigation on recurrent aphthæ no evidence of herpes simplex virus had been obtained. In a group of adults with recurrent aphthæ attempts to isolate virus at each successive recurrence were also unsuccessful. Three of these patients had no herpes-neutralizing antibody at the end of a three-year period.

CORRECTIONS

Section of Odontology—Meeting *November* 28, 1955, published in August 1956 *Proceedings.*

Ivor R. H. Kramer:

p. 546, lines 9 and 10.—For "In the cell shown in Fig. 1 a typical short pulpal process is seen" read "In the cell shown in Fig. 2 a typical short pulpal process is seen."

J. H. Hovell:

p. 555.—The legend to Fig. 6 should read: Radiographs of mandibular agenesis (traumatic). B: Before. A and C: After correction by iliac crest graft to ascending ramus.

Section of Obstetrics and Gynæcology

President—GERTRUDE DEARNLEY, M.D., F.R.C.O.G.

[*March* 23, 1956]

DISCUSSION ON NORMAL MICTURITION AND STRESS INCONTINENCE
[*Abridged*]

Further Observations of the Female Urethra and Bladder

By G. M. ARDRAN, M.D., D.M.R., J. HAMILL, M.A., B.M., D.M.R.D., and C. A. SIMMONS, M.A., F.R.C.S., M.R.C.O.G.

From the Nuffield Institute of Medical Research, Oxford, the X-ray Department the Oxford United Hospitals and the Institute of Obstetrics and Gynæcology, London

THE behaviour of the female urethra during barium urethrocystography as recorded on serial X-ray films taken up to 4 a second, in the lateral projection using an image intensifier has been described. The method and the findings in 27 patients have previously been published (Ardran *et al.*, 1956). The following conclusions were drawn:

(1) The urethra appears to be empty at rest except for a small "beak" of contrast medium projecting into the internal meatus.

(2) During straining the "beak" may increase slightly: in patients suffering from stress incontinence of urine the urethra may fill to a varying degree. On ceasing to strain the urethral contents are returned to the bladder.

(3) With interruption of the stream, the external sphincter closes first and the contents of the proximal two-thirds of the urethra are returned to the bladder by progressive obliteration of the lumen.

(4) A posterior urethrovesical angle of less than 180 degrees is usually present at the beginning of voiding in patients with or without stress incontinence of urine.

The present paper describes the observations on a further series of 24 patients examined in a similar manner (Table I) and 13 patients have had films repeated some nine months

TABLE I

	Previous series	Present series	Total
Subjects with No Disorders of Micturition			
Nulliparous. No operations	2	1	3
Parous. No operations	7	8	15
Previous P.F.R.	—	1	1
Previous Cæsarean section	1	—	1
12 weeks pregnant	1	—	1
Totals	11	10	21
Subjects with Stress Incontinence of Urine			
Nulliparous P.F.R. and sling	1	—	1
Total hysterectomy	—	1	1
Parous no previous operations	9	11	20
P.F.R.	5	1	6
Total hysterectomy	1	1	2
Totals	16	14	30
Patients re-examined after operation			13
Other studies			10
		Total studies made	74

after operation. 31 films on patients without, and 34 films on patients with stress incontinence, 64 patients, have been studied. In addition to these, 10 studies have been made on young boys and girls with disorders of the genito-urinary system. The previous conclusions have been confirmed; the method of closure of the urethra in the male has been observed to be similar to that of the female. The stream is "cut off" in the region of the membranous urethra and above this the contents are returned to the bladder and below are expelled out of the penile urethra.

The commencement of voiding.—Denny-Brown and Robertson (1935) showed that normal voiding is secondary to active contraction of the bladder. By voluntary restraint the

activity of the filled bladder can be inhibited. By lifting this restraint, active bladder contractions are facilitated and as the detrusor contracts the internal and external sphincters open reflexly. This has been observed and can take place without any downward movement of the bladder base; the urethra fills and the bladder commences to empty. Fixation of the diaphragm and contraction of the abdominal muscles are not necessary (Figs. 1 and 2).

The presence of a "beak" of barium at the internal meatus.—Most films show a small projection of barium at the internal meatus (Figs. 1 and 2). Table II shows the presence of

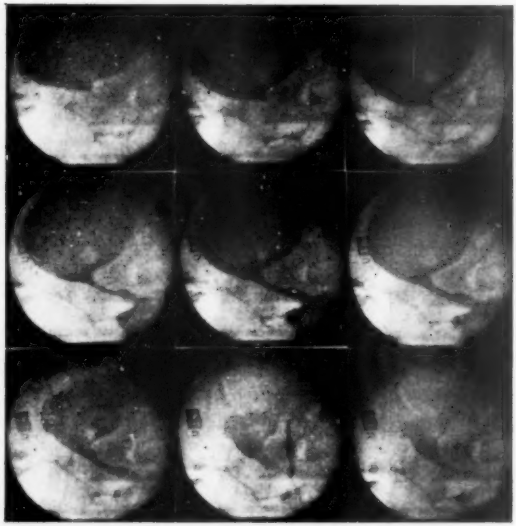


FIG. 1.—Serial films (from top—left to right) of a normal parous patient aged 31. *Top*: "Beak" at rest, commencement of voiding. *Centre:* Slight posterior urethrovesical angle during voiding. *Bottom:* The trigone area rises and the posterior urethrovesical angle is lost towards the end of the act.

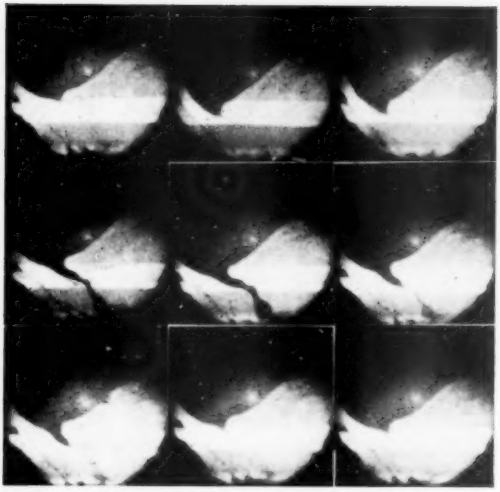


FIG. 2.—Serial films of a parous patient, aged 50, who did not complain of stress incontinence, but who admitted to it on occasions when standing. *Top:* the "beak" at rest and on straining. *Centre:* Voluntary interruption of the stream. The stream is cut off in the region of the external sphincter and the proximal urethra gradually empties its contents back into the bladder. The distal urethra is unusually dilated owing to a narrow external urethral meatus. *Bottom:* The bladder resumes its resting appearance.

a "beak" in patients with and without stress incontinence at rest and on straining. There was no correlation between the presence of a "beak" with stress incontinence (Table II). In patients without stress incontinence the beak, when present, while a little larger on straining, never passed the proximal third of the urethra except in one case. In patients with stress incontinence the contrast medium may pass to all lengths of the urethra but on ceasing to strain the urethra closed distally first, returning its contents to the bladder (Fig. 3).

TABLE II.—A "BEAK" OF BARIUM INDICATING THE INTERNAL URETHRAL MEATUS

		Barium not passing proximal third of urethra. At rest		Straining	
28 patients with no stress incontinence.		Beak present	Absent	Present	Absent
No previous operations	19	13	6	18*	1
Previous operation ..	9	3	6	7	2
Total	28	16	12	25	3
28 patients with stress incontinence		Barium passing to or beyond proximal third			
No previous operations	18	7	11	15	3
Previous operation ..	10	4	6	10	—
Total	28	11	17	25	3

*In one case barium passed the proximal third of the urethra.

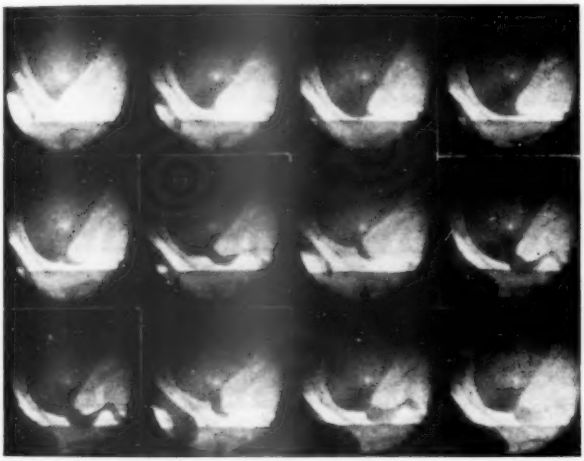


FIG. 3.—Serial films of a parous patient aged 47, with severe stress incontinence of urine. *Top:* Descent and forward movement of the internal meatus on straining. *Centre:* The whole urethra fills but on ceasing to strain the urethra is "cut off" at the external sphincter — voiding resumed. *Bottom:* Involuntary "cut off" and the resumption of voiding. There is a good posterior - urethro - vesical angle.

The presence of a "beak" and the desire to void.—35 patients were studied at rest (Table III). There appeared to be no relationship in patients with or without stress incontinence to the presence of a "beak" and the desire to void.

TABLE III.—THE DESIRE TO VOID AND BARIUM INDICATING THE INTERNAL MEATUS

		Beak present	Absent
19 patients with no stress incontinence			
Desire to void	16	6	10
No sensation	3	2	1
16 patients with stress incontinence			
Desire to void	14	4	10
No sensation	2	1	1
Total 35			
Desire to void	30	10	20
No sensation	5	3	2

Descent and forward movement of the bladder "neck".—Several observers have reported that on straining the bladder base and the posterior urethra move downwards and backwards. Table IV shows observations on 59 patients. Each patient was filmed while sitting and the

TABLE IV.—DOWNWARD AND FORWARD MOVEMENT OF THE BLADDER-NECK ON STRAINING

	Movement down		Forwards
29 patients with no stress incontinence	27	(gross in 4)	29
30 patients with stress incontinence	30	(gross in 6)	30

movement during coughing, straining and voiding was recorded. Downward movement of the internal meatus occurred in all and forward movement in all except two normal patients. Even gross movement occurred in patients with no symptoms. The movement was often greater on straining than on voiding (Fig. 3).

The presence of a cystocele.—A cystocele, while commoner in patients with stress incontinence, was often present in those without symptoms (Table V) and sometimes was very

TABLE V.—THE PRESENCE OF A CYSTOCELE

	At rest	Straining	Voiding
30 patients with no stress incontinence	5	20 (6 large)	6
The cystocele was obliterated during voiding in all but one			
33 patients with stress incontinence	15	31 (13 large)	12
The cystocele was obliterated during voiding in 7 and persisted in 5			

large. The large cystoceles in both groups were "taken up" as soon as voiding commenced in the majority of patients and only persisted during voiding in one patient without stress incontinence and in 5 patients with stress incontinence and gave the appearance of a "tea-pot" bladder (Fig. 4).

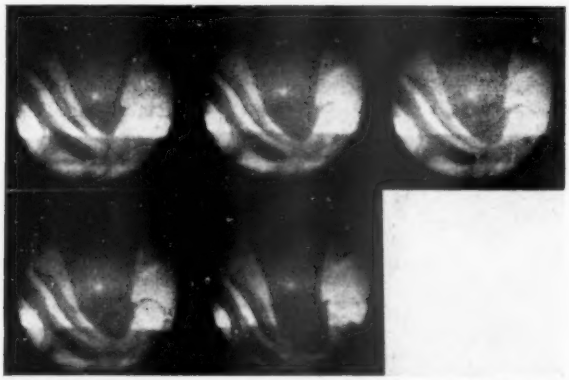


FIG. 4.—Parous patient, aged 52, with severe stress incontinence. Serial films, showing the whole urethra filling on straining. There is a large cystocele and rectocele giving the appearance of a "tea-pot" bladder. On ceasing to strain the urethra closes distally first.

The posterior urethrovesical angles.—As even a soft catheter can distort the urethra, which is not normally a straight tube, we have only been able to study the urethra on straining or voiding when filled with contrast medium without the use of a catheter. The angles have been classified into good, slight and nil. The slight ones are doubtful. Table VI shows that

TABLE VI.—THE POSTERIOR URETHROVESICAL ANGLE

			Good Angle	Slight Angle	No Angle
Control Series					
No previous operation.	Nulliparous	3	1	1	1
	Parous	17	8	6	3
Previous operation		11	8	1	2
	Total	31	17	8	6
Patients with stress incontinence					
No previous operation.	Parous	18	11	2	5
Previous operation		14	8	4	2
	Total	32	19	6	7

the urethrovesical angle as observed during voiding has no relationship to stress incontinence and that in the majority of patients with or without stress incontinence a good angle is present. Moreover the posterior angle may vary during emptying of the bladder, occasionally being present in one phase and absent in another. This would not be obvious in films taken with a "still" technique (Fig. 1). Similarly the size of the anterior angle could not be correlated with symptoms.

The junction of the distal third and proximal two-thirds of the urethra forms a relative fixed point in patients with or without stress incontinence. Downward angulation occurs here and the stream is cut off at this point when voiding is voluntarily (Fig. 2) or involuntarily (Fig. 3) interrupted. Occasionally the urethra appears as a straight line during some phase

of voiding, but we have been unable to correlate any angulation of the urethra itself with stress incontinence.

Delayed closure of the urethra.—If stress incontinence were due to a "weak" internal sphincter, possibly associated with over-activity of the detrusor, it was thought that this might be demonstrated by seeing how long it took the urethra to empty and return to its normal appearance on voluntary interruption of voiding. Contraction of the voluntary portion of the external sphincter can cut off the stream while the detrusor still contracts. By central inhibition of the detrusor activity the bladder relaxes and the urethra empties back into it. Films were taken at one a second for approximately 15 seconds after stopping voiding. A large "beak" remained in a few, but in the majority the bladder neck appeared as in the resting phase. There was no delay demonstrable in the cases of stress incontinence as compared with the normal (Fig. 2).

13 *patients examined before and nine months after operation.*—These patients were examined with special reference to the posterior urethrovesical angle as seen during voiding. Fig. 5

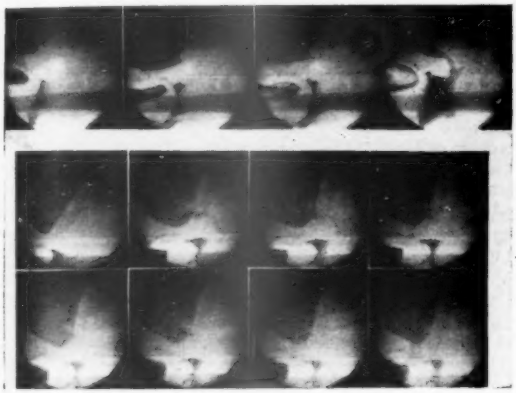


FIG. 5.—Parous patient, aged 36. Before and after a Manchester operation. She had no stress incontinence either before or after operation. *Top:* Before operation. At rest, straining and voiding. There is no posterior urethrovesical angle. *Centre and Bottom:* After operation. Commencement of voiding, voluntary stopping of the stream and gradual retraction of the residual "beak". There is a good posterior urethrovesical angle after operation.

is an example of a patient with no stress incontinence before and after a Manchester repair; there was no angle before operation and a good one after. Details of the findings are shown in Table VII. There appeared to be no relationship of the posterior urethrovesical angles to the cure of stress incontinence.

TABLE VII.—13 PATIENTS EXAMINED BEFORE AND NINE MONTHS AFTER OPERATION.

2 *Patients with No Stress Incontinence Before or After Operation*

Operation	Angle before	Angle after
Manchester (Fig. 5)	Nil	Good
Total hysterectomy and urethroplasty ..	Slight	Good

7 *Patients with Severe Stress Incontinence Cured After Operation*

Operations	No.
Abdominal hysterectomy and urethroplasty ..	1
Vaginal hysterectomy and urethroplasty	3
Manchester	2
Urethroplasty (previous Manchester)	1

The state of the angles	No.	Angle before	Angle after
	4	Good	Good
	2	Slight	Nil
	1	Nil	Nil

4 *Patients with Stress Incontinence Before and After Operation*
(of these 3 were greatly relieved)

Operation	Angle before	Angle after
Vaginal hysterectomy and urethroplasty ..	Nil	Slight
Vaginal hysterectomy and urethroplasty ..	Slight	Slight
Urethroplasty	Slight	Good
Urethroplasty	Nil	Nil

Comment.—Our number of cases is too small to draw any final conclusions, but it appears that stress incontinence may be due to either an over-active detrusor or to weakness of the

urethral sphincters. The fault may lie in either or both and may vary from individual to individual. If it is due to weakness of the sphincters, it would seem reasonable to attempt to strengthen these muscles by exercises of which asking the patient to practise stopping and starting the stream is the simplest.

No doubt a reduction of the laxity of the tissues around the urethra may assist in preventing its rapid or sudden overdistension and enable the sphincters to work to better advantage and this probably accounts for the success of the majority of repair operations. The sling operation may act in the same way or may only produce a stricture. Despite the undoubted success of certain operations there is doubt if they succeed for the reasons stated.

Control in the normal patient would appear to be due to the internal and external sphincters of the urethra. However, the external sphincter is not composed solely of the voluntary compressor urethræ, for in the male, upward obliteration of the urethra above the membranous portion must be due to contraction of the urethral wall itself within the prostate. Our evidence indicates that the female urethra behaves in the same manner. This portion of the external sphincter is stated (Bucy *et al.*, 1937) to be innervated by the sympathetic system and has been observed to contract on stimulation of the distal end of the cut presacral nerve in a male subject and to grip the cystoscope so tightly that it could not be moved. It appears therefore that almost the whole of the urethra acts as a long sphincter which opens reflexly when the detrusor contracts. The voluntary portion of the external sphincter innervated by the pudendal nerve can reinforce the action of obliteration, or hold the stream when the internal sphincter is still open and the detrusor is contracting. After interruption of the stream, as the detrusor relaxes, the urethra is obliterated progressively, the external sphincter closing first and the contents of the proximal two-thirds of the urethra being returned to the bladder. If the whole urethra fills when a subject with stress incontinence strains, obliteration occurs in a similar manner on ceasing to strain.

Acknowledgments.—We would like to thank Mr. J. Stallworthy and Mr. W. Hawksworth and their assistants of the Area Department of Obstetrics and Gynæcology, Oxford, and our other colleagues for their continued help in allowing access to their patients. We should also like to thank the Director and Staff of the Institute of Obstetrics and Gynæcology, London, for allowing one of us (C.A.S.) the opportunity to take part in this work.

REFERENCES

ARDRAN, G. M., SIMMONS, C. A., and STEWART, J. H. (1956) *J. Obstet. Gynæc., Brit. Emp.*, **63**, 26.
BUCY, P. C., HUGGINS, C., and BUCHANAN, D. N. (1937) *Amer. J. Dis. Child.*, **54**, 1012.
DENNY-BROWN, D., and ROBERTSON, E. G. (1935) *Brain*, **56**, 189.

Bladder Control in the Female

By T. N. A. JEFFCOATE, M.D., F.R.C.S.Ed., F.R.C.O.G., and H. ROBERTS, M.D., M.R.C.O.G.

From The Department of Obstetrics and Gynæcology, The University of Liverpool

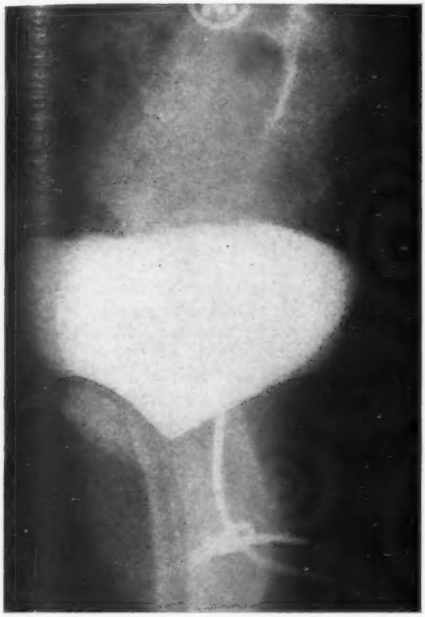
IT has been suggested that although many workers have confirmed our radiological findings in respect of bladder function and stress incontinence (Jeffcoate and Roberts, 1952, 1954; Roberts, 1953), others including those at Oxford, have made contrary observations. Any differences, however, are apparent rather than real and are easily explained by : (i) Misunderstanding or overlooking what we have previously written; (ii) Failure to appreciate the traps and difficulties of cysto-urethrography with resulting erroneous interpretation of the films.

Our views are based on a study of 485 *series*[1] of radiographs obtained from 382 patients in our own hospital. The original fully documented 206 cases with 281 series of cysto-urethrographs were re-examined by Mr. H. Roberts for the purpose of this paper.

Cysto-urethrography in the continent woman.—The bladder base as seen from the side in the normal woman is more or less flat with an upward slope towards the sacrum (Figs. 1 and 2). There are, of course, variations; sometimes it is more horizontal while a downward sagging in the middle line is not uncommon, especially in multiparæ. Our experience, like that of Ardran *et al.* (1956) has always been that cystocele is more apparent on radiological than on clinical examination. The axis of the normal urethra is comparatively straight and it joins the bladder base with clearly-defined angles before and behind. The presence of the posterior urethrovesical angle is typical of normal sphincteric control of the bladder but *it is not the angle itself which provides continence: the angle is merely a radiological sign that the so-called internal sphincter is competent.*

The term "angle" refers only to a silhouette; it has been used for want of a better. We have described it only in general terms such as good, moderately good, poor and absent.

[1]Each series comprises at least 3 and usually more films.



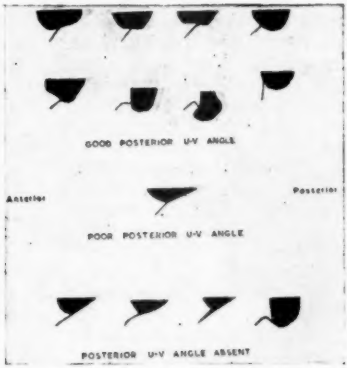


FIG. 2.—Examples of different types of posterior urethrovesical angle.

← FIG. 1.–Cysto-urethrograph of normal nulliparous woman standing and straining. The bladder base slopes backwards and slightly upwards. The urethra makes clearly defined anterior and posterior angles with the bladder base.

Note the lateral pouch which, super, imposed on the floor of the bladder-appears to alter the shape of the latter.

Moreover, the exact shape of the angle varies enormously (Fig. 2). These variations have no special significance and all that matters is that the trigone of the bladder and the floor of the urethra are not in a straight line.

The angle, and therefore an efficient urethrovesical junction, is present in most but not all of *presumably* continent women (*see* Table I). There are, as we have always maintained,

TABLE I

	Number of patients	Posterior U–V angle lost at ease or on straining	Posterior U-V angle *seen** at some time during micturition usually late
Normal nulliparæ	23	1	5
Normal multiparæ	14	3	4
Prolapse without stress incontinence ..	33	1	18 (72% of 25†)
Stress incontinence	136	119 (87%)	12 (10% of 122†)

*Only the positive findings are significant because, when using still radiography, seeing the angle is somewhat fortuitous.

†Micturition films were not obtained in all cases.

exceptions and the significance of these can only be appreciated if a sufficiently large number of normal women are studied. Here there is difficulty because many "normal" women if questioned closely will admit to occasional stress incontinence. Nemir and Middleton (1954) found that more than 50% of 1,327 unmarried nulliparous college women had occasional incontinence and in 5% it was a *frequent* occurrence.

When the continent woman, no matter whether she has prolapse or not, raises the intravesical pressure by bearing down strongly the shape of the urethrovesical junction does not alter significantly. Continence is always maintained at this level and bladder fluid does *not* enter the urethra (Figs. 1 and 6).

During micturition the levatores ani relax as the abdominal muscles contract and this allows a downward movement of the upper urethra and bladder which rotate around a fixed point at the triangular ligament. Coincident with this movement, or possibly as a result of its trigger action, the detrusor muscle of the bladder contracts; this is made manifest radiologically by an ovoid shape to the bladder and by crenations seen best on the outline of its posterior wall (Fig. 3). The bladder has a property of polarity similar to that of the

uterus and contraction of the detrusor is accompanied by dilatation of the urethra which opens from above downwards. The last part of the urethra to open is that which is surrounded by the voluntary compressor urethræ and nervous inhibition of micturition is in large part explained by failure of this muscle to relax. Indeed this muscle is so strong that it can prevent evacuation even when the detrusor of the bladder is still contracting (Roberts 1953).

The opening of the upper urethra is characterized by maintenance of the anterior urethrovesical angle while the posterior angle disappears to bring the trigone of the bladder and the floor of the urethra more or less into line. When micturition is well established, the posterior urethrovesical angle is sometimes partly restored (Fig. 4, Table I). Indeed, in a nervous woman in whom micturition is not proceeding smoothly it sometimes does not disappear at all. If, during voiding, a woman is told to stop the act she contracts the compressor urethræ and interrupts the stream at the level of the triangular ligament (Fig. 5). The urethral fluid is then returned to the bladder as the urethra gradually closes.

Restoration of the normal anatomy of the urethrovesical junction is one of the last features of micturition and, according to all the evidence available at present, *is the result of contraction of intrinsic muscle* (? *involuntary* ? *voluntary*) *in the area*, and not of the contraction of the levatores ani. This last point we have hitherto deduced from indirect evidence but we suspect that the Oxford films demonstrate it.

Cysto-urethrography in stress incontinence.—The *most constant* anatomical abnormality associated with stress incontinence is loss of the posterior urethrovesical angle on straining, and sometimes even at rest (Fig. 2). Two points deserve emphasis:

(1) Loss of the urethrovesical angle is a feature of only approximately 90% cases of stress incontinence (Table I): our original estimate of 80% deliberately erred on the conservative side (Jeffcoate and Roberts, 1952). Exceptions are explained by rigidity and fibrosis of the urethral muscles and possibly by other lesions (Jeffcoate and Roberts, 1954).

(2) Not all women who lose their posterior urethrovesical angle suffer from stress incontinence. Their bladder control is not perfect although it is adequate and is explained by total urethral resistance and by use of the compressor urethræ in emergency.

The urethral muscles below the urethrovesical junction *provide a second line of defence* so that, if a woman who suffers stress incontinence has a warning that she is about to cough or to sneeze, she can sometimes hold the urine in the urethra returning it to the bladder when the crisis has passed. Although they were not taken with this matter specially in mind, our films show that *at least* 9% of women with stress incontinence can do this.

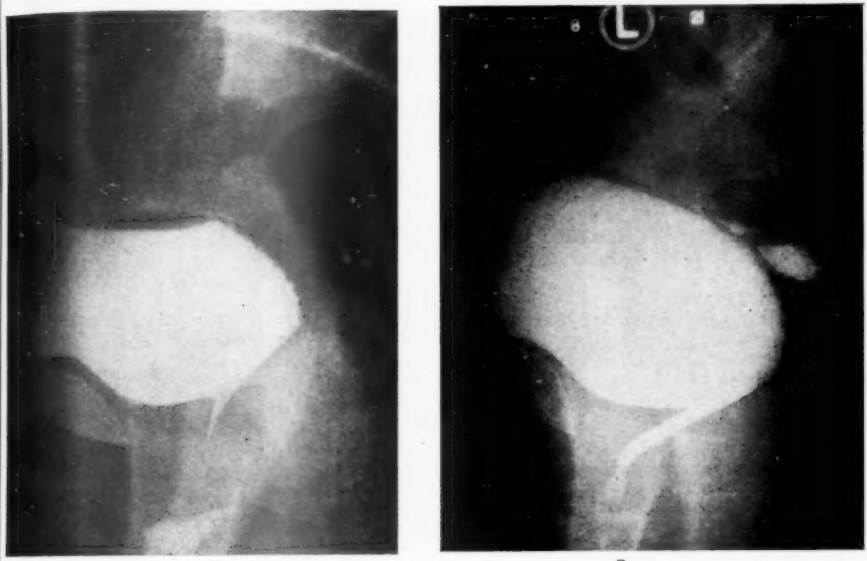
This explains why operations which succeed only in buttressing the urethra and in tightening its musculature can improve stress incontinence without restoring the posterior urethrovesical angle. Control of the bladder is not perfect but it is good enough for most occasions.

The technique and interpretation of cysto-urethrography.—Outlining the urethra with a soft rubber catheter filled with radio-opaque fluid is open to the criticism that the method disturbs the normal shape and direction of the urethra. It certainly prevents study of the *shape* of the lower urethra but *our cysto-urethrographs taken during micturition are without any object other than voided fluid in the urethra* and these confirm its overall straightness and direction.

Unless some sort of marker is used for the urethra the site of the urethrovesical junction can only be guessed and the guess can be surprisingly inaccurate. Ardran *et al.* (1956) were able to identify the internal meatus by a slight "beak" of radio-opaque substance. This beak is quite an exceptional finding in our experience and it is not hidden by a catheter (Fig. 6).

Cysto-urethrography requires *personal attention* to each case and has many traps for the unwary (*see* Fig. 7). Misleading appearances include the following: (1) The lateral extensions of the bladder are sometimes lower than the trigone and, when seen from the side, are easily mistaken for an unusually-shaped bladder base (Figs. 1 and 7) (*see also* the second Fig. 1 of Ardran *et al.* (1956). (2) The patient fails to bear down when told to do so or the film is not exposed at the moment when she is straining so the X-ray appearance which is said to represent stress is that of the resting bladder and urethra (Fig. 7A). This error is the more likely in cases of stress incontinence when the woman is afraid of "an accident". (3) Some women when told to strain, deliberately or unconsciously initiate the process of micturition and thus obliterate the posterior urethrovesical angle and produce a false appearance of the anatomy of stress incontinence (Fig. 7B). This happening is easily recognized from the shape of the bladder as a whole and from the crenations on its outline. (4) Filling of the bladder with radio-opaque material can itself induce detrusor contraction and consequential changes in the urethrovesical junction. This possibly explains why in the only two nulliparous women studied by Ardran *et al.* (1956) they obtained radiographs which purport to show the normal bladder with the patient at rest or straining but which in fact show the early

stages of micturition. The crenations caused by detrusor contraction are clearly shown in their published radiographs.



A B

FIG. 3.—Micturition in normal nullipara. A, The urethra opens from above downwards by obliteration of the posterior urethrovesical angle. Note the crenations on the posterior wall of the bladder which denote detrusor contractions. B, Micturition well established. The bladder base and upper urethra have moved downwards and backwards to angulate the urethra at the triangular ligament. The ovoid shape of the bladder and the crenated posterior margin denote detrusor contractions. The shadows behind the bladder are incidental being caused by lipiodol in the peritoneal cavity from previous hysterosalpingography.

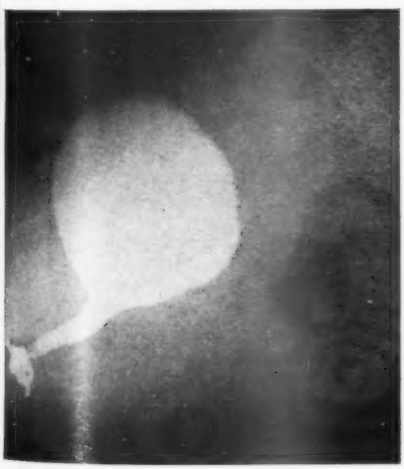


FIG. 4.—Hesitant micturition in a nervous woman with partial restoration of the posterior urethrovesical angle.

FIG. 5.—Two exposures superimposed to show voluntary arrest of micturition by the compressor urethræ with return of fluid to the bladder.

This technical problem is related to the *speed* at which the bladder is filled, to the *extent* of filling and to the *temperature* of the fluid (Roberts, 1952*b*). The amount of fluid which

ordinarily produces an urge to micturate is 250 to 300 ml.—the amount of radio-opaque material which Ardran *et al.* (1956) usually used "to produce a sensation of fullness". In nervous women it requires less than this and in all women *rapid* filling causes detrusor activity. It was because of this that we long ago altered the amount of fluid to 160 ml. for the average case, allowing it to enter very slowly and at body temperature, and even withdrawing some if the patient says the bladder feels full.

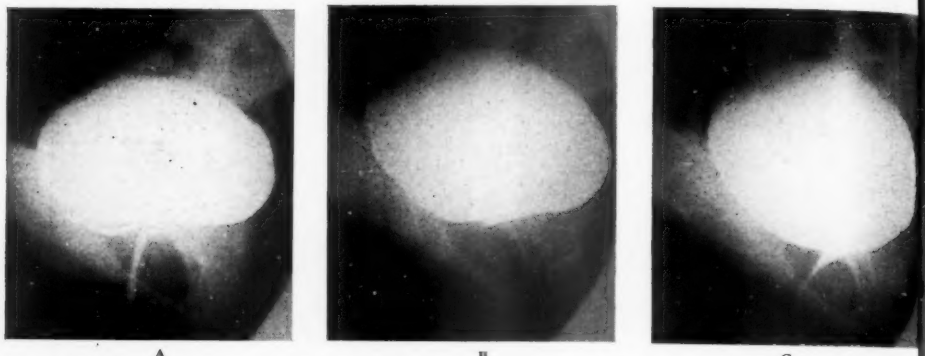


FIG. 6.—Cysto-urethrography using half-strength Micropaque as a medium. Normal nulliparous woman. A, Catheter in place but "beaking" at the internal meatus can be seen. The posterior urethrovesical angle is normal. B, Patient straining, catheter extruded. The "beak" is present as before and the posterior angle remains. "Beaking" almost invariably occurs if a large amount of half-strength Micropaque is used. C, Early micturition showing the urethra opening from above downwards and a reasonably straight urethra.

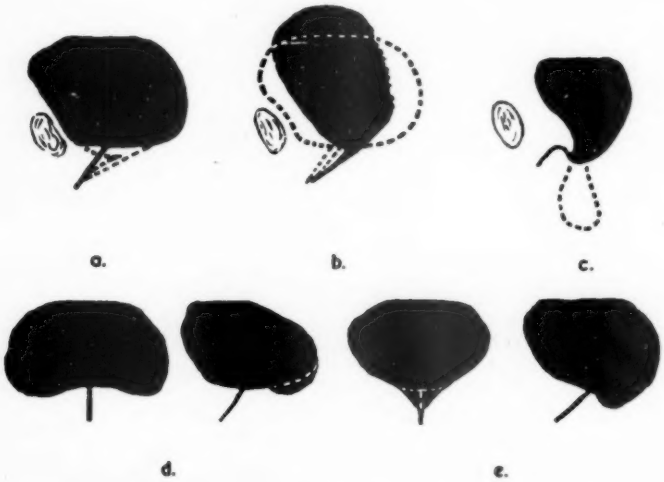


FIG. 7.—Diagrams illustrating common mistakes with cysto-urethrography. A, Patient fails to raise intravesical pressure so the appearance is that of the resting bladder and loss of angle is not seen. B, Patient micturates instead of bearing down and produces a false impression of loss of angle. The shape of the bladder and the crenated outline are the clues to recognition of this occurrence. C, False picture of absent posterior urethrovesical angle caused by the patient failing to fill the lower part of a large cystocele. D, The posterolateral extensions of the bladder can, when seen from the side, give a false picture of the shape of the floor of the bladder. E, Cystocele and other lesions give a false picture of funnelling in anterior-posterior radiographs.

Certain radio-opaque fluids and objects may be more liable than others to induce bladder activity. For example, a coil of chain as used by Hodgkinson (1953) and Kennedy (1955)

or a balloon as employed by Ball (1950) and by Youssef and Mahfouz (1956) lies on the extremely sensitive trigone and is likely to stimulate it. Half-strength Micropaque itself is suspect. It weighs one and one-third times as heavy as does urine and 12·5% sodium solution, the weights of 300 ml. of these fluids being: urine 339 grams, sodium iodide solution 342 grams, half-strength Micropaque 453 grams. Whatever be the operative factor, we have been able to show in each of three normal nulliparæ investigated in the last two weeks that the Oxford technique induces a "beak" at the internal meatus which is not present with sodium iodide solution (Fig. 6). Moreover, two of these women could not avoid initiating micturition when told to bear down.

So important is it to ensure that the technique is correct and that the patient obeys instructions that it is essential for a gynæcologist or interested radiologist to be with the patient at the time of radiography. Nevertheless, when it comes to micturition, a man should not be allowed within sight of the woman otherwise she nearly always fails to pass urine freely.

These and other technical problems make cysto-urethrography of limited value as a practical day-to-day procedure for the busy and harassed gynæcologist or radiologist but they should not be allowed to detract from its intrinsic merit as a means of studying bladder and urethral function under properly-controlled conditions. The application of cine-radiography to this field offers many avenues of investigation but the two which come immediately to mind are (1) the relationship between restoration of the posterior urethro-vesical angle and the contraction of the pelvic floor, and (2) the speed at which the angle can be obliterated or restored when the patient is nervous; this might give a guide as to whether it is voluntary or involuntary muscle which is concerned in the maintenance of the angle.

Figs. 1 and 3A are reproduced from the *Journal of Obstetrics and Gynæcology of the British Empire* (1952*a*), and Fig. 3B from the *American Journal of Obstetrics and Gynecology* (1952*b*), by kind permission.

REFERENCES

ARDRAN, G. M., SIMMONS, G. A., and STEWART, J. H. (1956) *J. Obstet. Gynæc., Brit. Emp.*, **63**, 26.
BALL, T. L. (1950) *Amer. J. Obstet. Gynec.*, **59**, 1243.
HODGKINSON, C. P. (1953) *Amer. J. Obstet. Gynec.*, **65**, 560.
JEFFCOATE, T. N. A., and ROBERTS, H. (1952*a*) *J. Obstet. Gynæc., Brit. Emp.*, **59**, 685.
——, —— (1952*b*) *Amer. J. Obstet. Gynec.*, **64**, 721.
——, —— (1954) *Surg. Gynec. Obstet.*, **98**, 743.
KENNEDY, W. T. (1955) *Amer. J. Obstet. Gynec.*, **69**, 338.
NEMIR, A., and MIDDLETON, R. P. (1954) *Amer. J. Obstet. Gynec.*, **68**, 1166.
ROBERTS, H. (1952*a*) *Brit. J. Radiol.*, **25**, 253.
—— (1952*b*) M.D. Thesis. University of Liverpool.
—— (1953) *J. Obstet. Gynæc., Brit. Emp.*, **60**, 621.
YOUSSEF, A. F., and MAHFOUZ, M. M. (1956) *J. Obstet. Gynæc., Brit. Emp.*, **63**, 19.

Professor R. J. Kellar, *Department of Obstetrics and Gynæcology, University of Edinburgh:*
Some three years ago a group of us decided to re-examine **Certain Problems of Micturition in the Female.**

The Anatomy of the Urethra

At the beginning of our joint studies we had with us in Edinburgh Dr. Willi Langreder, now Dozent in Gynæcology in the University of Mainz. Dr. Langreder undertook to re-examine the anatomy of the urethra, and the following is a brief account of his work. Dr. Langreder's complete descriptions have appeared (1956) in *Zbl. Gynäk*, **78**, 561.

It is generally believed that the urethra regulates the passage of urine through its lumen by passive enlargement and active contraction of its muscular components. Disturbances of urethral function, unlike those, say, of the cervix, arise almost entirely with failure of the closure mechanisms.

The Intrinsic Structure of the Urethral Wall

(1) *The urethral epithelium. Epithelial folds and glands.*—This factor in the closure mechanism is often overlooked. It has its origin in the tissue turgor of the more superficial cells and possibly in the interlocking of the longitudinal epithelial folds. In its inner third the urethra is lined with transitional epithelium similar to that of the bladder and the epithelial folds are not very marked. In its middle third the epithelial folds show an increasing development.—The outer third of the urethra—the pars navicularis—is lined with an epithelium similar to that of the vagina and this can be shown to undergo cyclical changes. Simple cytological studies based on urethral smear preparations show that the cells are scanty and of basal type in the immediate pre-menstruum, in the postpartum period and after the menopause. This component of urethral closure might be significantly weakened at these times and it is well known that stress incontinence is not infrequently observed at

these periods. The occasional success of œstrogens in ameliorating the symptom is probably due to its effect on the urethral mucosa.

(2) *The urethral submucosa.*—The structures promoting urethral closure in the submucosa are the collagenous and elastic connective tissue and the venous plexus which is found in this area. The elastic tissue itself may be sufficient to effect closure when the resting tonus in the bladder does not exceed more than a few centimetres of water. The role of the peri-urethral corpus cavernosum is not quite clear. If the surrounding tissue preserves adequate tone then adequate vascular filling will have a closing effect. On the other hand, if the muscular layer has poor tone vascular engorgement might well have the opposite effect of enlarging the urethral wall by stiffening the lumen.

(3) *The intrinsic musculature of the urethral wall.*—This is, of course, by far the most important factor in the closure of the urethra, yet is the one which is least understood and about which there is the greatest divergence of opinion. The two main views are as follows: Some believe that there is an anatomical circular internal sphincter at the cysto-urethral junction and this was the view of Zangemeister, Kelly and Stœckel. Others believe that there is a type of internal sphincter formed by two half-rings or loops and this arrangement is depicted by Martius in his well-known and frequently-copied illustration.

Our dissections would appear to show that neither of these views is correct. Dissections carried out with the aid of the low power microscope and a study of histological preparations show that, in fact, the unstriped muscle of the bladder continued down the urethra in the form of interlacing spirals and these can be traced as far as the external meatus. This apparently complicated arrangement is a well-recognized structural principle of many other hollow muscular organs. Adjacent to the spiral muscular fasciculi are the inner and outer longitudinal layers, and that part which is continuous with the longitudinal layer of the trigonum is particularly well developed. The function of these longitudinal layers is of the greatest importance for, according to their contraction or relaxation, they affect the spirals of the rest of the intrinsic layer. If they contract they flatten the spirals so that they act for all intents as circular sphincters. If the longitudinal layers relax the spirals tend to be unwound and this gives rise to the typical funnelling effect seen at the onset of micturition. These variations in the spiral muscle explain how in the past they have given rise to the impression that there is a circular sphincter or a loop arrangement at the internal meatus.

The integrity of these muscle layers is of the greatest importance in urethral closure and it is a well known clinical observation that stress incontinence may not be present in patients who show the most severe damage to the other urethral supporting structures presumably because the intrinsic musculature is relatively undamaged.

The Fixing Structures Around the Urethra

It is convenient to refer to the tissues supporting the urethra as the para-urethrium. None of these individually is as important as the intrinsic musculature, but defects in the supports may cause a somewhat damaged intrinsic musculature to become incompetent. In the nullipara the anterior edge of the levator ani muscle has a very close relationship to the urethra. Even after childbirth with the inevitable separation of the muscles fascial attachments between the muscle and the urethra can be demonstrated. Functionally the levator ani muscle can compress the neck of the bladder from side to side as well as elevating and closing the urogenital hiatus. Reflex contraction of the levator will assist in adequate closure of the urethra and methods of improving the activity of the muscle by controlled exercises are often successful in improving, if not curing, the symptoms of stress incontinence. Reflex levator spasm is often the cause of retention following pelvic floor operations.

There has been much dispute as to the existence in the female of a urogenital diaphragm and the external sphincter to be found in it. Histologically it is possible to demonstrate in the middle third of the urethra the presence of striated muscle bundles. Most of these appear to cross the anterior surface of the urethra and are generally absent from the posterior wall. Thus although striped muscle does exist in the middle third of the urethra it is difficult to visualize the tissue as a true sphincter. The muscle tissue would appear to have the effect of pulling the urethra down, possibly against the contracting levator ani muscle.

The bulbo cavernosus muscle can have but a modest part to play in supporting the urethra. Probably a few fibres are picked up when a bridge of supporting tissue is being built up under the urethra.

The strongest attachment of the urethra is to the symphysis pubis—the pubo-urethral ligament of Delbet. This ligament will support a weight of a kilogram without tearing and even in the most advanced cases of prolapse this attachment remains unaffected, and it is seldom necessary to deal with this part of the para-urethram. The attachment of the lower part of the urethra to the structures of the vulva is of importance in that this is a point of urethral fixation and damage to these attachments must affect the length of the urethra. This area is not suitable, however, for operative repair. There are close connexions between

the vagina and the urethra and some vaginal muscle fibres surround the urethra and decussate between the vagina and urethra. It is possible to speak of a vaginal urethral sphincter. Directly and indirectly, the para-urethral tissue is connected to the paracolpos and parametrium and operations designed to improve the supports of the uterus will indirectly benefit those of the urethra. Long unstriped muscle fibres run between the cervix and urethra and are more or less continuous with those derived from the antero-vaginal wall; these constitute the pubo-cervical fibres of Victor Bonney. These fibres are fixed together with those of the upper part of the trigone to the anterior part of the supravaginal cervix and it is only when this attachment is incised that the bladder can be swept off the cervix. The normal attachments of this tissue would appear to be responsible for the normal angulation of the urethra and bladder. When the muscle is stretched normal angulation is lost and can only be restored by operative procedures designed to tighten this layer of muscle and its attachments. Finally in dealing with the para-urethram we might mention that in cases of prolapse there is always present some shortening of the urethra and this shortening takes place from above. This shortening disturbs the normal relationships between the trigonal and urethral muscles and restoration of the length of the urethra can be achieved only by raising the level of the bladder as is done in the Manchester type of operation or by one of the sling types of operation.

It is extremely difficult to assess the relative importance of the various components of the para-urethram in maintaining the urethra in its correct position. It is clear that the most important single factor in maintaining adequate closure of the urethra is the integrity of the muscular relationship between the trigone and the urethra. Without this, stress incontinence will result no matter how the structures of the para-urethram attempt to compensate.

Observations on the Habits of Micturition in the Healthy Female

At first we classified the symptoms of stress incontinence in the order of severity: Grade I stress existed when the patient had occasional incontinence with severe stress and with a full bladder; Grade II when there were more frequent episodes with marked stress, and Grade III when the patient was incontinent with mild stress and irrespective of the fulness of the bladder. Over a period of three years some 30% of patients admitted to my wards confessed to Grade I stress when asked about it. Many of these women suffered from prolapse and so to settle this point Professor A. S. Duncan undertook to inquire into the habits of micturition in a group of healthy nurses working at his hospital and thus determine the incidence of stress incontinence in nulliparous young women.

150 nurses were asked to fill in a questionnaire. Naturally, no physical examination was carried out. 134 replies were received; 100 of these were from women under the age of 30 and all were nullipara. Out of 134 nurses, 87 confessed that they experienced leakage on stress from time to time; in 70 it was of occasional occurrence but in 17 it was frequently experienced. In general, stress incontinence was most likely to occur when the bladder was full, the nurse standing and suddenly laughing, coughing or sneezing. Somewhat less than half of those experiencing stress incontinence also from time to time experienced urge incontinence.

Professor Duncan's analysis, therefore, made it clear to us that stress incontinence is of frequent occurrence in young nullipara and that our Grade I group could be abandoned. We adopted the simple classification of moderate and severe stress incontinence depending on the nature of the stress and the frequency of the incontinence. Presumably the incidence in parous women of similar age would be substantially higher.

Observations on a Group of Patients Specially Studied

These patients were highly selected. Many were problem cases who had had one or more pelvic floor operations. Others complained of mild stress incontinence; others again were virtually incontinent. In all, 70 women were fully studied and in most cases dealt with operatively. Let me briefly refer to certain points in ætiology.

All but 3 of our patients were parous women and of these 50% had had an instrumental delivery or had given birth to a child weighing more than 9 lb. In general, there was little relationship between the severity of the stress incontinence and the degree of cysto-urethrocele present. A quarter of the patients were post-menopausal when the symptom began to give rise to trouble but 3 nullipara were still menstruating.

The majority of women who have severe stress incontinence also complain of urge incontinence particularly when rising in the morning: "early morning urge incontinence". Dysuria was a most uncommon symptom and only two of these 70 patients had a bacilluria. Frequency was a very common occurrence and was thought often to be a conditioned prophylactic measure to avoid leakage.

The pelvic floor.—We were impressed by the fact that in the majority of patients suffering from severe stress there was a wide separation of the anterior margins of the levator muscle. In the majority of patients voluntary contraction of the muscle was minimal, perhaps 5–10

mm.Hg at the first reading obtained by the perineometer. A great deal of time was spent on teaching these women to contract these muscles, and we had the full co-operation of the physiotherapists. These latter were taught to palpate the levator muscle and by means of this and the Kegel perineometer patients were often able to improve the readings up to 30–40 mm.Hg. Unsupervised and unmeasured pelvic floor exercises are largely a waste of time. Cystometry and cystoscopy were carried out in all our patients but gave little help. We had some 500 films to examine, anterior and lateral views with the bladder and urethra shadowed, and in general we were able to confirm the modern views on the alterations of the anatomy of the bladder neck in terms of the junction of the urethra and bladder. It must be stated, however, that in a third of our patients the posterior vesical angle did not disappear on straining. We were not impressed by the change in the radiological picture in those patients who had been successfully operated on, and we have examples of cure with a lost angle and failure with a good angle. The radiological pictures are confessedly difficult to interpret and it may be that we were not sufficiently skilled to do so.

Observations on the Treatment of Stress Incontinence

In the vast majority of cases stress incontinence can only be cured by operation but conservative measures must not be lost sight of. Controlled pelvic floor exercises, we feel, are a most important part of the pre- and post-operative treatment. The judicious use of œstrogens in post-menopausal patients and attention to the diet in the overweight patient play a rôle. The psyche does affect this symptom and we are all familiar with the variation in the severity of symptoms that can be caused by worry and nervousness. A simple dilatation and curettage can effect at least a temporary cure in some cases! Our colleague Dr. W. A. Liston cures many of his patients by exhortation and suggestion, but I do not know how permanent the cure is.

No one can guarantee to cure a patient of stress incontinence by a vaginal plastic operation of the classical type. 50 patients who complained of stress incontinence and prolapse in 1949 were subjected to operation. In 1955 when these patients were seen personally by my colleague Dr. Donald Irvine, an absolute five-year cure rate of only 50% was found. In discussing so-called cures in relation to stress incontinence it is always necessary to specify the number of years since operation. Clearly a patient who is suffering from some degree of genital prolapse in association with stress incontinence requires a vaginal plastic operation but in addition some special measures must be taken to correct the stress incontinence. This may vary from a simple Kelly stitch to a sling operation, or one of the many operations designed to sling and buttress the urethra. I have found the simplest method is one employing the nylon net ribbon introduced by Professor Anselmino. The whole operation takes little time and can easily and safely be added to a prolapse operation. The small suprapubic incision gives rise to no trouble. Formerly I used a free fascia lata sling but I do not think that this has any advantage over the nylon ribbon. What I am certain of—and I know my colleagues in this study agree with me—is that the only way one can be certain of curing a genuine stress incontinence is by some form of simple sling operation or its equivalent.

Section of Laryngology

President—W. A. MILL, M.S., F.R.C.S.

[*March* 2, 1956]

DISCUSSION ON CANCER RESEARCH: ITS PRESENT TRENDS

Professor A. Haddow (Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital): *The Study of Carcinogenesis*

There are many possible approaches to the cancer problem but the study of carcinogenesis is one of the most central and important.

It is just over forty years since cancer was first induced by experimental means by the Japanese, through the application of carcinogenic coal tar to the ears of rabbits. Many years have been spent in developing that key observation, but during the last ten years we have concentrated much more upon problems of the mechanisms of action of cancer-producing substances: by their use we can convert the normal cell into a cancer mutation. So far as we can make out there is no essential reason why ultimately the whole of that process should not be defined in biochemical terms. That process has just started to be elucidated, and eventually it may be the only rational approach to the whole cancer problem.

Twenty-three years ago my predecessors at the Royal Cancer Hospital identified the hydrocarbon 3 : 4-benzpyrene as the substance responsible for the introduction of skin cancer through occupational exposure. Very soon afterwards large numbers of related compounds were synthesized in the laboratory and over a period of years Kennaway and his school were able to work out a fascinating series of relationships between these compounds, with reference to the parent hydrocarbon phenanthrene. A great deal of work has been carried out to determine which feature of these molecules is the most significant, and the research work by the French school of theoretical physics indicates that a special part of the molecule, the phenanthrene double bond, is of great importance for the induction of the carcinogenic process.

In spite of our considerable knowledge of the relationship between chemical constitution and biological action, we still have no inkling as to the site within the cell at which these substances combine and operate, nor do we know exactly by what means they bring about carcinogenic transformation. However, in the past five to seven years we have been studying carcinogenic activity in an entirely different class of chemical substance, namely, the so-called nitrogen mustards which contain a nitrogen atom to which are attached two chloro-ethyl side-chains of the same kind as those found in mustard gas. We were struck by the fact that the biological activity of these compounds is closely related with chemical reactivity. This was a feature which had already been suspected in the case of the carcinogenic hydrocarbons, but is more evident here.

These, then, are substances which in some ways are much more readily susceptible to investigation than the hydrocarbons, which are sluggish and complex and do not themselves suggest any likely method of action. An essential feature in these new carcinogens is the presence of the two highly reactive side-chains. These substances also act directly upon the dividing cell and their cytological effects—for example, chromosome fragmentation, the production of bridges at anaphase, and interference with the process of chromosome spiralization—can be studied with relative ease.

Many of these effects can be mimicked by ionizing radiation. There is a certain parallelism between the effects of the hydrocarbons and that of ionizing radiation, but the parallelism is much closer in the case of the mustards, which can induce biological end-results indistinguishable from those due to X-rays. Examples are greying of the hair in coloured mice, the application of certain of these agents in the palliation of Hodgkin's disease and the chronic leukæmias, and the carcinogenic properties which many of them, equally, possess.

At an early stage in the study of the nitrogen-mustard-induced tumours we were struck by the appearance in the tumour cells of anomalies of cell division rather similar to those produced by the same compounds in normally dividing cells. This feature drew our attention more and more to the possibility that such agents may act primarily on the cell nucleus. While the primary action may well be on the nucleus it must be understood that that would at once involve repercussions in the cytoplasm, and more recently we have been giving attention to possible consequent changes in the cell surface.

After studying several hundred such compounds it became obvious that biological activity in these series depended on the presence of at least two of the characteristic side-chains, and the question arose why that should be so. It was suggested by three of my colleagues at the Cancer Hospital that the requirement might be based upon a so-called cross-linking mechanism. We now know that the hypothesis is unduly simple. Nevertheless

it immediately led to much further work along two lines. First of all, cross-linking chemical agents, already used in the textile industry in the treatment of wool to prevent shrinkage and to improve fabrics, were tested biologically. It became at once obvious that many such agents, developed for industrial purposes, did in fact bring about biological responses in dividing cells equivalent to those produced by the mustards and by radiation.

Apart from selecting agents already known, great efforts were made to synthesize entirely new kinds of compound which might be expected to show this kind of biological activity in enhanced degree. Most of these efforts were quite unsuccessful, as usually happens, but in one case success was achieved, namely, in a series containing methanesulphonyloxy groups. Members of this series proved to be similar in action to the others we had already studied, but in addition some showed new and relatively specific properties—namely, in their capacity to reduce the number of circulating neutrophils. One such compound was, accordingly, subjected to clinical trial with special reference to chronic myelogenic leukæmia and this agent (Myleran) can produce useful responses in this disease.

On the fundamental side we do not know chemically with which of the cell receptors these agents combine, but high in the list of possibilities there are the nucleic acids. Here we are dependent upon advances in the knowledge of these substances before we can proceed farther. This field has been tremendously influenced in the last eighteen months or two years by the proposal made by Watson and Crick as to the structure of deoxyribonucleic acid (DNA). While awaiting further knowledge as to the receptors involved (and especially as to the chromosome structure itself) we can obtain a good deal of information from study of what is still the most favourable biological material in that respect, namely, the giant chromosomes of the salivary gland of the fruit fly drosophila.

Many of the present facts and observations tend to support an older view, namely, that the change from the normal to the malignant cell may involve a process of biological loss. At the moment, we imagine that the carcinogens may act by deleting proteins or enzyme systems which may be concerned with the regulation or the damping down of more primitive reactions which, left to themselves, drive the cell into division. If this is so, it may be possible eventually to attain a kind of substitutive chemotherapy, by which the growth of the malignant cell may be restrained once more by treatment with the enzyme systems in which it is defective. At the moment we regard the essential change as a kind of specific biochemical deficiency, and the next stage is to establish its exact nature more precisely.

Professor Geoffrey Hadfield (Imperial Cancer Research Fund, Clinico-Pathological Laboratories, Royal College of Surgeons): *Co-carcinogenesis*

I shall consider the part played by research in the problem of malignant disease arising in protective epithelia, i.e. the skin and the upper respiratory, upper gastro-intestinal and lower genito-urinary tracts.

In these situations it is often possible to relate the malignant process to a predisposing factor and if many cases are grouped together on this basis it becomes obvious that such factors as chronic disease, occupation, personal habits, atmospheric pollution and physical environment carry a significant carcinogenic risk.

As examples of such "populations at risk" one may quote the male Chinese population of Malaya, the shale-oil workers of East Lothian, the mule spinners of South East Lancashire, men having syphilitic glossitis, middle-aged women suffering from dysphagia and chronic microcytic anæmia, as well as the population of heavily industrialized areas, and I would suggest that the investigation of indirect carcinogenic risks such as these should be regarded as an integral part of fundamental cancer research. There is little doubt, for example, that the inorganic salts of arsenic are carcinogenic to man, although experimental animals are insusceptible to them. The fact that there are 72 occupations in which this human carcinogen is employed is a piece of highly significant ætiological evidence. In those whose work involves the use of chromium salts primary cancer of the lung is 16 to 80 times more common than in the general population and there are approximately 50 occupations in which these substances are used. The number of occupations in which crude tar is employed is of the same order.

When cancer of protective epithelia is viewed against this background it seems permissible to make certain generalizations. In the first place a long latent period varying from five to twenty years elapses before malignant disease declares itself (*see* Fig. 1), and the exposure to the carcinogenic environment need not, after this period of initiation, be continuous. Secondly, the proportion of those exposed to the risk who develop malignant disease is small compared with the total population subjected to the same hazard.

If we use these generalizations to plan a realistic experiment we might assume that the carcinogenic agent is acting at a sub-carcinogenic level and that, in all probability, most of the human population at risk is resistant, possibly highly resistant, to its action. In our experiment, therefore, we should employ our carcinogen in sub-carcinogenic doses over

a long period, take great care to avoid producing malignant change and use an animal which is fairly resistant to our carcinogen.

When these conditions are fulfilled it has been shown that *the whole epithelial surface subjected to continuous sub-carcinogenic doses of carcinogen becomes profoundly altered.* In the language of the experimentalist it is "initiated" and becomes highly "reactive" for if a relatively small part of it, selected at random, is appropriately stimulated, a carcinomatous focus will develop where the specific stimulus is applied. The localized production of malignant disease in an initiated surface is known as "promotion" and this can be induced by the application of another carcinogen in sub-carcinogenic doses or by using a weak carcinogenic agent such as croton oil. On the other hand, non-carcinogenic irritant chemicals, ultraviolet light, heat below 100° C., and solid CO_2 are, to varying degrees, all capable of promoting malignant disease in initiated surfaces. More significantly, however, simple excision of a relatively small part of the area promotes malignancy more frequently than physical and chemical injury, more especially when the animal used is, like the rabbit, less susceptible to the pure coal-tar carcinogens than a highly susceptible animal such as the mouse. In this connexion it may be supposed that man more closely resembles the more resistant rabbit, for it is well established that the rhesus monkey possesses a high degree of natural resistance to these potent carcinogens. In a significant number of experiments, when a rabbit skin area, such as the pinna, is initiated by sub-carcinogenic doses of a pure coal-tar carcinogen the only way in which malignant disease can be promoted in it is to punch out a cylinder of skin and underlying tissue. This manœuvre was introduced by Peyton Rous, and one of his experiments is illustrated in Fig. 2. A long period of initiation by the applica-

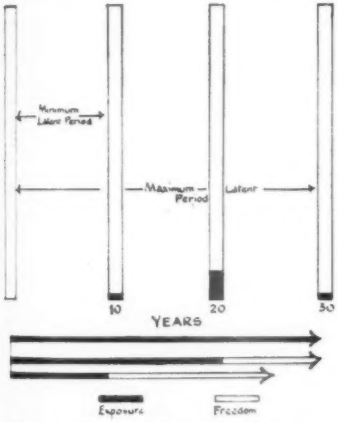


FIG. 1.—General characters of development of cancer of protective epithelia (skin, upper respiratory and digestive tracts). *Vertical unshaded columns:* Population at risk. Dark segments: Number of cancers developing. *Horizontal columns:* Dark—continuous exposure. Light—periods of freedom.

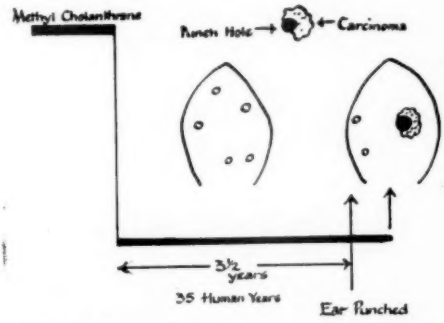


FIG. 2.—Peyton Rous experiment. Skin of pinna of a rabbit "initiated" over a period of twelve "human years" followed by an interval of "freedom" for thirty-five "human years," at the end which the ear was punch-holed and a carcinoma developed at the edge of the hole in a relatively short time.

tion of methylcholanthrene to the animal's ear produced a series of regressing papillomata (unshaded circles). After a period corresponding to thirty-five years of human life a hole (black circle) was punched in the ear and during the healing process a focus of infiltrating carcinoma appeared at the edge of the hole. The fact that carcinoma of an initiated surface can be promoted by another carcinogen raises the rather strong probability that these agents may act synergistically in the strict pharmacological sense. Reduced to everyday experience we may suppose that, in this age of industrialism, a man whose occupation exposes him to a carcinogen in sub-carcinogenic dose may develop a carcinoma because another carcinogen, acting below the threshold dose, is added to the industrial process in which he is engaged, or that he changes his occupation to another in which a dissimilar carcinogen is used.

The unsolved problem of the nature of "initiation" is a challenge which has been taken up by many research workers. Berenblum, a pioneer in this field, suggests that there is a profound change of growth habit in the basal or germinal cells of initiated epithelia. He would have us believe that differentiation is inhibited in the daughter cells derived

from proliferating basal cells and that initiated epithelia contain an excess of undifferentiated cells possessed of considerable growth potential. Cancer arises when such cells are propelled into continuous mitotic division by a promoting agent. Orr, on the other hand, suggests, and has produced supporting evidence, that the primary effect of initiation is on the sub-epithelial mesenchyme.

It may be that human pathology has a contribution to make in this controversy. An increasing number of pathologists are being converted to a belief in the reality of the lesion known as carcinoma *in situ*, or intra-epithelial carcinoma. In the vaginal portion of the uterine cervix this lesion is said to precede the development of infiltrating cancer by a period of years. Under the guidance of Dr. J. Bamforth I have learned to regard this lesion as having distinctive histological characters and Dr. Bamforth is encountering an increasing number of instances in the course of his work in the Clinico-pathological Laboratories of the Imperial Cancer Research Fund. The multiple lesions of chronic arsenical dermatitis and their progress to carcinoma *in situ* and infiltrating cancer afford a striking demonstration of the increased cellular reactivity of a surface epithelium "initiated" for long periods of time by a carcinogen in subcarcinogenic doses.

In conclusion, I would suggest that the general terms of the hypothesis of "initiation and promotion" are sound, that detailed investigation of other "initiated" epithelia would provide useful evidence and probably help us to understand the early pathogenesis of carcinoma in epithelial surfaces exposed to the hazards of a carcinogenic environment.

Dr. P. R. Peacock (Cancer Research Department, Royal Beatson Memorial Hospital, Glasgow):

Two main trends in cancer research are of particular interest to me. The first is towards more detailed knowledge of the intimate life of cells and involves the techniques of tissue culture, virology, and electron microscopy on the morphological side, and of biochemistry and organic and theoretical physical chemistry on the analytical and deductive side. These techniques are practically limited to small groups of specialists. The second is based on demographic and geographic peculiarities in the incidence of human cancer and the experimental assay of suspected environmental carcinogenic factors deduced from such studies. It is this second line of work which I shall discuss.

The early work of Hoffman in America and of Stevenson, Cramer and others in Great Britain drew attention to the great difference in site incidence in different groups of people, and these may be summarized as follows:

(1) The total incidence of cancer in man is much the same in all countries where the expectation of life is comparable.

(2) The site incidence often differs between such groups, e.g. in Scandinavian countries cancer of the stomach is about twice the incidence found in Great Britain.

(3) Within the same country the different socio-economic groups differ in regard to cancer of some exposed sites, e.g. skin and upper alimentary canal; but not for others, e.g. lungs and rectum.

(4) An increasing number of industrial and environmental carcinogenic hazards are known.

Some of the commonest sites of cancer in man are rare in most other animals, e.g. cancer of the stomach and of the lung.

3 : 4-Benzpyrene is formed when organic matter is destructively distilled with incomplete oxidation and is found in coal-tar, pitch, soot, and in atmospheric pollution from such sources, and must have been a common human environment for many centuries, particularly in towns.

Apart from the use of organic fuel for heat and power, some kinds of cooking and smoking afford other examples of pyrolysis of organic matter and merit further consideration, for whereas almost all people in so-called temperate zones are subject to atmospheric pollution, the exposure to environmental factors of cooking and smoking vary considerably.

For example, frying, grilling and roasting cause different chemical reactions from boiling or stewing. Not only so, but the vessels used for cooking can play an important part in the chemical changes involved. Iron is a potent catalyst for heated fats and induces more vigorous reactions than, for example, aluminium or glass. The nature of the changed products is not fully understood but polymerization occurs and a number of polymers are under suspicion as potential carcinogens.

Whatever the chemical nature of the end products, cottonseed oil heated to 320° C. in the presence of iron is more carcinogenic for the forestomachs of mice than the same oil heated in glass vessels without contact with iron. Thus such a simple change in human habits as the increasing use of non-ferrous cooking vessels might have an influence on the incidence of gastric cancer, if the human stomach reacts in the same manner as the fore-stomach of the mouse, though we have no means of being sure about this.

Smoking presents a much more difficult problem to the experimentalist, though the issue is more clear-cut than any other human environmental factor outside certain industrial hazards. The association between cigarette smoking and lung cancer seems to be established beyond all reasonable doubt, though the causal nature of the association has not been proved. The presence of 3 : 4-benzpyrene in cigarette smoke reported by Cooper *et al.* (1954, *Chem. & Ind. (Rev.)*, p. 1418) has been confirmed by Lyons (1956, *Nature, Lond.*, **177**, 630) in my Department, but the quantity is not large compared with that present in the atmosphere of industrial areas.

To double the annual intake of 3 : 4-benzpyrene from atmospheric pollution a town dweller would have to smoke about 60,000 cigarettes a year. On the other hand, to double the quantity of airborne arsenic only 100 to 150 cigarettes need to be smoked.

While it is difficult to eliminate ordinary atmospheric pollution as a factor in the experimental study of lung cancer, it can be achieved for small rooms fitted with efficient ventilating plant. Thanks to a generous loan of an electrostatic precipitator by Professor Mayneord, we are able to maintain a colony of mice in an almost soot- and dust-free atmosphere, for comparison with a genetically similar colony in an adjoining room with unfiltered air.

About 20% of untreated mice over 1 year of age have adenoma or adenocarcinoma of the lung in our animal house and it will be interesting to see whether the colony in the cleaner atmosphere shows any reduction in this incidence.

Other species of laboratory animals rarely develop tumours of the lungs or bronchi.

The problem of exposing animals to tobacco smoke under conditions resembling those of the human habit is not an easy one. The following desiderata must be met: The smoke should reach the animal's lung in intermittent puffs with free access to relatively pure air between exposures. The distance travelled by the smoke should be about 6–12 in. from cigarette to lung as in the human. The exposure should not cause contamination of the whole animal or of its food with smoke. The animal should be relatively free from spontaneous lung cancer but susceptible to it when exposed to a carcinogen.

To meet these requirements as far as possible we have used fowls which we have shown to develop cancer of the bronchus after exposure to 2-acetylaminofluorene, but which rarely develop spontaneous cancer of respiratory system.

For experiments on atmospheric pollution we use mice in two rooms with different levels of atmospheric soot by filtering the air in one room and blowing in the unfiltered air of the centre of Glasgow in the other.

Dr. Peacock concluded by projecting a film which shows the anatomy of the respiratory system in the fowl and a simple technique for pumping cigarette smoke through the air sacs and lungs. Details of this work have already been published (Peacock, 1955, *Brit. J. Cancer*, **9**, 461). It will be some years before we can assess the influence of the habit on these amiable and co-operative birds.

Dr. R. L. Worrall: A recent trend in cancer research is seen in attempts to check malignant growth by the administration of fat antioxidants, such as tocopherols, gallates and other substances used in food preservation. These attempts are based upon the assumption that something is radically wrong with fat metabolism in cases of cancer.

In a healthy individual, stored or circulating neutral fat is an unoxidizable food reserve, unavailable as such for cell nutrition. Irradiation, however, whether with X-rays or products of atomic fission, can initiate the abnormal process of fat autoxidation. This process is self-perpetuating, and may continue spontaneously for months or years, since it occurs through uncontrolled chain reactions. Irradiation, which is a potent cause of cancer, thus tends to induce a self-perpetuating metabolic disorder.

Elsewhere, I have presented evidence indicating that localized autoxidation of neutral fat constitutes an abnormal source of auxiliary nutriment for cancer cells, while having a detrimental effect on normal cells. This conclusion emerges from a study of myeloid leukæmia, where early disappearance of marrow fat is an outstanding accompaniment of the malignant growth of white cells in the bone marrow.

The widely accepted "somatic mutation" hypothesis of cancer is now somewhat threadbare. As an alternative, I have suggested that carcinogenesis is a heritable cell adaptation to an abnormal biochemical situation, namely neutral fat autoxidation, induced by irradiation or by specific chemical compounds.

Using this possibility as a working hypothesis, one can narrow the choice of compounds, for experimental cancer chemotherapy, to those substances which are known to react with products of neutral fat autoxidation. Various antioxidants, designed to prevent peroxide formation, have not checked malignant growth in experimental animals, and compounds of another class offer greater promise. Applying the principle, set a thief to catch a thief, one can administer peroxide-forming compounds, such as those found in the volatile oils, in order to set up catastrophic reactions in cancer cells.

Treatment of human cancer cases with these peroxide-forming compounds is in fact already in progress, and details of the theory and practice of this new trend in cancer research are available.

Mr. Musgrave Woodman said that he was particularly interested in the preparation of the chromosomes. Professor Haddow's attention had been largely devoted to experimenting with carcinogens and he hoped that some day he would produce something which would put their reaction into reverse and clean up cancer rather than produce it.

Dr. Peacock had said that the last function of the cell was to multiply. How often one had seen an apple tree, when getting old, throw out more and more apples every year in a last effort to propagate.

Mr. S. W. Allinson said that at a research centre in New York he had been shown the experiments carried out with purine derivatives. They cultivated cancer cells *in vitro* and treated them with various purine derivatives. Photography with the electron microscope showed that the cancer cells were destroyed whereas the normal tissue was not destroyed. He wondered if any work was being done with purine derivatives in this country.

Professor Haddow, in reply to Mr. Allinson, said that much work was going on in this country in the field of metabolic antagonists, with special reference to anti-folic, anti-purine and anti-pteridine agents.

[*May* 4, 1956]

THE following papers were read: **Ectopic Salivary Adenomas,** by Mr. KENNETH HARRISON and Dr. HELEN M. RUSSELL[1]; **Four Cases of Identical Tumour associated with the Infra-orbital Nerve,** by Mr. F. C. W. CAPPS and Professor GEORGE CUNNINGHAM (to be published in the *Journal of Laryngology and Otology*).

The papers were discussed by Mr. F. B. COCKETT, Mr. E. D. D. DAVIS, Mr. DOUGLAS RANGER, Mr. MAXWELL ELLIS, Mr. R. G. MACBETH, Mr. T. LEVITT and Dr. I. FRIEDMAN.

[1]*see* Harrison, K. (1956) *Ann. R. Coll. Surg. Engl.*, **18**, 99; Russell, H. (1955) *Brit. J. Surg.*, **43**, 248.

[*June* 14 and 15, 1956]

Section of Laryngology with Section of Otology

JOINT SUMMER MEETING HELD AT THE GENERAL HOSPITAL, NOTTINGHAM

LARYNGOLOGICAL SESSION

[*June* 14, 1956]

Chairman—W. A. MILL, M.S., F.R.C.S. (President of the Section of Laryngology)

THE following papers were read and will be published in the *Journal of Laryngology and Otology:*

The Present Place of the Laryngofissure Operation by Mr. T. O. HOWIE. Those taking part in the discussion were: Sir VICTOR NEGUS, Mr. MAXWELL ELLIS, Mr. F. McGUCKIN, Mr. G. H. BATEMAN, Professor I. SIMSON HALL, Mr. R. G. MACBETH, Mr. R. D. OWEN, Mr. P. H. GOLDING-WOOD, Professor VICTOR LAMBERT, Mr. F. C. W. CAPPS and the CHAIRMAN. Mr. HOWIE replied.

The Changing Aspect of Nasal Disease by Mr. J. H. OTTY The following took part in the discussion: Mr. F. C. W. CAPPS, Mr. J. B. M. GREEN, Mr. T. J. WILMOT, Professor I. SIMSON HALL, Mr. S. W. ALLINSON, Mr. A. G. GIBB, Mr. R. L. FLETT, Mr. H. S. KANDER, Mr. E. J. GILROY GLASS, Mr. J. W. S. LINDAHL, Mr. E. G. COLLINS, Mr. E. P. BLASHKI, and Mr. OTTY replied.

OTOLOGICAL SESSION

[*June* 15, 1956]

Chairman—E. G. COLLINS, F.R.C.S.Ed. (President of the Section of Otology)

THE following papers were read and will be published in the *Journal of Laryngology and Otology:*

Secretory Otitis Media by Mr. G. H. BATEMAN. The following took part in the discussion: Mr. R. J. CANN, Air Vice-Marshal E. D. D. DICKSON, Mr. P. G. SCOTT, Mr. F. McGUCKIN, Mr. E. P. BLASHKI, Mr. J. W. S. LINDAHL, Mr. I. G. ROBIN, Mr. A. G. GIBB, Mr. MAXWELL ELLIS, Mr. F. C. W. CAPPS, Mr. MYLES FORMBY, Mr. E. J. GILROY GLASS. Mr. BATEMAN replied.

The Significance of the Circulation in Some Inner Ear Diseases by Dr. J. C. SEYMOUR. Mr. T. J. WILMOT, Sir VICTOR NEGUS and the CHAIRMAN contributed to the discussion.

Section of Physical Medicine

President—J. SHULMAN, M.B., Ch.B.

[*March* 14, 1956]

DISCUSSION ON POSTURAL RE-EDUCATION—A CRITICAL EXAMINATION OF METHODS

Dr. Basil Kiernander: For the purpose of an evaluation of this kind it is first of all essential to appreciate what is meant by the term "good posture" and the factors that are necessary for the maintenance of posture.

Posture Definitions and Study

Through the ages many attempts at defining good posture have been made. The ancient Greeks considered athletes to have the perfect posture and portrayed the beauty of the human form in their pictures and sculpture. Unfortunately, studies of the modern athlete show us that even the most skilled may possess postural defects. In modern times artists have portrayed the human body as they see it without considering its functional efficiency. The physical educationalists have varied immensely in their approach to correct posture and have been influenced by many factors including the æsthetic and medical, and for a time favoured the military carriage so popular in the Armed Forces of many countries earlier this century. Anatomists have regarded correct structure as being the right basis for posture and the clinicians have been primarily interested in the abnormalities of posture in relation to disease.

Appleton (1950) described good posture as one in which the body functions best; and he further defined it as one which best resisted disability, either as an immediate consequence or long-term result, whereas he regarded faulty posture as one which precipitated or predisposed to disability. Steindler (1955) quoted a simple definition by Goldthwait (1909) of a good posture as one in which the head was held erect, chest forward, shoulders drawn back and abdomen retracted, with the two most essential relations being that of the spinal column to the line of gravity, with its conventional levels of intersection at the cervico-dorsal, dorsi-lumbar and lumbo-sacral joints, and that of the pelvis to the cardinal transverse plane of the body.

From America the White House Report (1932) recommended the term "Body Mechanics" as being preferable to "Posture".

It is impossible for all persons to assume identical attitudes and it is undesirable to attempt to achieve a single, standard, correct posture.

Burt's (1950) description of a rough test for good posture was the suspending of a plumb-line from the tip of the mastoid process which should pass through the greater tuberosity of the humerus, the great trochanter of the femur and a point 1½ in. in front of the lateral malleolus. He also mentioned a second extremely simple criterion for correct pelvic carriage, viz. the upper end of the cleft of the buttocks should be at the same vertical level as the back of the heel, whilst Appleton (1944, 1946) regarded the limits of normality for the inter-gluteal cleft as varying from 2 in. in front to ½ in. behind the back of the heel. Burt also quoted a cervical kyphosis as being present if the occiput were more than 2 in. in front of the gluteal cleft, a cervical lordosis if the occiput were more than ½ in. behind the gluteal cleft and the dorsal curve of the spine as being abnormal if the most prominent part were more than ½ in. behind the gluteal cleft. The average pelvic angle as measured by Appleton from the anterior superior iliac spine to the posterior superior iliac spine is 5 degrees to 10 degrees, whereas Wiles (1937) in his measurement of the angle between the upper part of the symphysis pubis in front and the posterior superior iliac spine behind, averaged 30 degrees.

Mechanical Defects

The factors adversely affecting the maintenance of correct posture are, first of all, any mechanical causes in the locomotor system itself. These vary from a wide range of congenital defects which may be in any part of the skeletal or central nervous systems—for example, congenital hemivertebræ, the commonest cause of structural scoliosis in children, and the results of birth trauma, such as account for certain cases of torticollis—to a multiplicity of other conditions, congenital or acquired, of which a typical example, acquired and persisting in later life, is the shortening of a leg as a result of anterior poliomyelitis. In all these cases of mechanical defects of a structural nature it will be essential to correct them with appropriate appliances or surgical help before any hope of a permanently correct posture can result.

Other mechanical causes can be produced as the result of many pathological processes of a more general nature, for example, muscular hypotonia is often the result of general

debility or other disorders, and if the muscle tone is inadequate to maintain a correct posture as the result of such underlying disease, that latter disease must be treated in the first instance. Mechanical causes from outside the body may, of course, produce comparable postural defects; for example, tight clothing in childhood can be sufficient to prevent the respiratory excursion of the chest developing to the full and this may predispose towards winter coughs in children and even chronic bronchitis in later life if neglected. Ill-fitting shoes may be responsible for producing defects in the feet and secondary defects elsewhere.

Psychological Defects

The second, and perhaps the most important, factor is the psychological one. An individual's mood is shown in his posture: The erect carriage and speedy movements of the happy person are shown at one end of the scale while the depressed or melancholy patient, with his drooping posture and retarded movements, is an example at the other end. Before going into the other factors in postural defects, this side must always be explored fully, inasmuch as even a temporary psychological upset will very frequently produce a deterioration in posture. The child who has an unhappy home or is unhappy at school, or even one who has had a conflict with his family, friends or colleagues at work, will show this in a variety of postural defects, and unless the psychological difficulties are corrected he will not improve. The important therapeutic measure here, in addition to correcting any conflict which may be present, is to make the individual proud of his correct posture and his physical development. In this context I will be mentioning later that the time when postural defects become most manifest in city dwellers is between the ages of 15 and 18, and it may well be that the tendency to-day for so many of the youths after leaving school to become Teddy Boys and slouch round the streets is symbolized by their slack posture. The relationship of this to activities in the sporting sphere has its psychological aspect as well.

General Health

The general health of the patient plays an important part in the maintenance of posture. After any debilitating disease the patient tends to have a poor posture, and with his return to well-being so will his posture improve.

Faulty Habits

Postural defects often arise purely as the result of faulty habits, and an interesting example of these was demonstrated by Wesson (1938) when he described the clinical syndrome of "shop assistant's hip" where, as the result of a faulty stance at work, many girl shop assistants tended to stand with one knee partially flexed, and the opposite hip became unduly prominent with a compensatory scoliosis. This even produced in some cases abdominal pain simulating appendicitis. Dentists tend to develop a scoliosis with rotation after long hours standing over the dental chair. Various unsuitable desks and chairs for office workers have also resulted in a variety of postural defects, particularly the development of kyphosis and kypho-scoliosis, often seen amongst young draughtsmen. Even the excessive pursuit of one particular sport may predispose to postural errors, e.g. one sometimes finds them in cyclists who develop a dorsal kyphosis from long periods of bending over the handlebars.

Types of Defect

I divide postural defects into static and dynamic. The static defects consist of those observable when the patient is in a resting position, either sitting or standing, and the defects will generally be multiple. For example, defects of the feet and ankles, such as flat feet and valgus ankles, may be responsible for a complete upset of posture and produce secondary defects of posture such as knock-knees and curvatures of the spine. This makes it absolutely essential, when examining for postural abnormalities, to have any child or adult completely undressed apart from pants or swimming trunks.

Amongst the many authorities classifying postural defects, Burt (1951) selected as the commonest: (*a*) lumbar lordosis, (*b*) shop girl's hip, (*c*) flat back, (*d*) sway back, (*e*) dorsal kyphosis and (*f*) poking chin. Wiles (1949) regarded postural defects as having two components: (*a*) increase or decrease in pelvic inclination and (*b*) dorsi-lumbar kyphosis. Table I shows his results:

TABLE I

Increased	pelvic inclination	+ mobile spine: Lumbar lordosis.
Increased	pelvic inclination	+ dorsi-lumbar kyphosis: Sway back.
Decreased	pelvic inclination	+ mobile spine: Flat back.
Decreased	pelvic inclination	+ dorsi-lumbar kyphosis: Round back.

If neglected, these defects may be followed by backache and pain in the limbs as the result of fatigue and postural inefficiency. They also predispose to osteo-arthritic changes, especially in the spine.

The dynamic postural errors consist of those observable in function, for example, walking

and breathing, and can also arise from faulty habits. These also predispose to complications later in life, e.g. inadequate expansion of the lungs associated with recurrent upper respiratory infections in children may lead to stagnation of inspired mucopus at the bases, and consequently these children become prone to winter coughs and may even develop chronic bronchitis or bronchiectasis in later life.

Treatment

The treatment of both these static and dynamic postural defects consists of making the individual concerned aware of his errors, and in training him in the voluntary correction thereof. He should be taught to carry out his exercises with such frequency and enthusiasm that his new correct posture becomes habitual. In the case of children the parents and school-teachers must be taught how to supervise the exercises and be made responsible for so doing. It is useless for a child merely to do exercises two or three times weekly at a clinic or at school without carrying them out with adequate frequency each day at home. Remedial exercises can be employed from the day after birth onwards, and the earlier correct treatment of postural defects is instituted the more effective and rapid will be the results. In early life, however, the remedial programme is somewhat different from that of the adult. Infantile gymnastics are based on reflex action and are of particular value in the treatment of scoliosis, torticollis and muscular hypotonia. From the age of 12 or 18 months play-movements are employed therapeutically, and when a child reaches the age of 4 years or so it is possible to take advantage of his intelligent co-operation.

Incidence of Postural Defects and the Results of Treatment

The White House Report in 1932, which described a careful survey of the incidence of postural defects in American school-children, produced a statistical picture which has not varied up to the present. The children studied in this series were some 1,700 in number and were divided into children provided with individual remedial postural exercises, where necessary, and a control series without these. Both the specially treated and the control series were given a normal physical training programme in school. It was shown that 92% of the children had faulty postures at the beginning and 44% of these had extremely bad postural defects. After one school year with remedial exercises for the individual postural defects, 62% had improved in posture, 1% had regressed and 37% remained *in statu quo*. In the control series only 10% had improved, 23% were worse and 67% remained *in statu quo*. In the four grades of posture that were used in this classification, it was found that after one year 63% of the children in the postural class had moved up one grade compared with 10% in the control class; 24% in the postural class had moved up two grades as compared with 1% in the control class, and 8% in the postural class had moved up three grades as compared with 0% in the control class.

It was found that regression might occur in one year after the school holidays if the child were not kept at his exercises, but that there would be improvement again during the second year. It is uncommon for regression to occur after two years. The total study showed that less than 5% of postural defects could not be improved by training, and nine times as many children improved with postural training as without.

Organized games have only a limited value and tend only to help those already well-developed. The child with a poor physique is generally not a good games player and for that reason is not keen at games and is therefore left in the background. On the other hand, the child particularly well-developed physically in one or more directions is keen to play games at which he already shines.

In looking at children of various ages in this country, I have found that the figures I have collected in a much smaller series are comparable with the White House figures. There is also a very detailed report on the school-children of Tottenham published as the Roper Report (1948), and this is well worth careful study. In my experience the child, on leaving school, often ceases to be posture-conscious and deterioration starts then.

Anna Broman in 1933 quoted a study of 1,600 British elementary school-children with 85% defective postures and also a series of 700 blind school-children with 75% defective postures. Phelps and Kiphuth (1932) quoted as follows:

TABLE II

5,250 subjects		12 and under	13 to 18	18 onwards
Group I	Good	1·6%	3·32%	2·31%
Group II	Fair	93·6%	92·54%	84·64%
Group III	Poor	4·8%	4·12%	13·0%

In those leaving school at 15 and not participating in any sporting activities thereafter, the incidence of postural defects rises to over 90% by the time of National Service at the age of 18. The B.M.A. Physical Education Committee in 1936 produced figures from the

largest survey ever conducted in this country, covering 720,000 boys; only 38,000 of them indulged in physical activities and at least 72% did not take part in any.

In the study made by myself and my colleagues in the R.A.F. on the posture of airmen, our figures confirmed that deterioration in posture occurred after leaving school at the age of 15—especially in those individuals who had not indulged in any form of active physical exercise or postural training. I can only give figures for a cross-section of 100 airmen on entry into the recruiting depot and after watching them over a two months' period of training including remedial postural training. In this series 50% had left school at 15 and only one-third of these airmen had played games thereafter, those with the better posture falling into that category. On entry approximately 95% showed some postural defects, 70% of these having a scoliosis and 15% an associated kyphosis, these being chiefly boys who had followed a sedentary occupation, including draughtsmen. Some 80% of the recruits showed a generally poor muscle tone and power with inadequate respiratory movements. Only 3 in 100 showed good physical development and these were all good games players. After eight weeks' training 70% only showed postural defects.

I would now deviate to mention the findings in cadets at the R.A.F. College at Cranwell. The numbers in this series are too small to be statistically significant but on entry the cadets showing physical defects were approximately 66%. A number of the cadets had already been carrying out postural training in other branches of the R.A.F. before being selected for admission to Cranwell. With the intensive programme of physical and postural training provided there over a year the incidence of defects fell to 50% or less and remained at about that level, but it must be appreciated that after the first year at Cranwell the amount of time available for postural training is materially diminished.

It will be seen from this main summary that the best results ensue from making the individual aware of holding himself correctly and encouraging him to take an active part in games both during and after his school period. On the whole people living in the country tend to have better postures than those living in cities, but where the city dwellers' programme of physical and mental education is well organized and includes individual postural training the school child's posture is good. It is not until after leaving school that the degeneration occurs.

The measures required in treatment therefore are to make the individual proud of his correct posture and keen to take an active part in sports and games, and to stimulate him to have the right psychological outlook on life. This, indeed, is the policy of various organizations, and especially the Central Council for Physical Recreation.

One must have the correct psychological background, freedom from disease, good hygienic surroundings and dietary and pride in the maintenance of good posture.

I am grateful to the Director-General of Medical Services of the R.A.F. for permission to publish the R.A.F. figures, and to the Headquarters Staff of the Central Council of Physical Recreation for kindly providing me, as one of their Medical Advisory Panel, with a large volume of bibliography which would have been quite unobtainable from any other source.

REFERENCES

APPLETON, A. B. (1944) *J. Phys. Educ.*, **32,** 5.
—— (1946) *Practitioner*, **156,** 48.
—— (1950) In: British Surgical Practice (edit. Carling, E. R., and Ross, J. P.). London; **7,** 20.
Body Mechanics: Education & Practice (1932) White House Conference on Child Health and Protection. New York; **3,** 90.
British Medical Association. Physical Education Committee (1936) Report, 18. London.
BROMAN, A. (1933) Posture and Posture Training. Ling Physical Education Ass., London; p. 16.
BURT, H. A. (1950) *Proc. R. Soc. Med.*, **43,** 187.
—— (1951) Some effects of faulty posture. Report of a Conference on School Remedial Work. Ling Physical Education Association, London; p. 8.
GOLDTHWAIT, J. E. (1909) *Boston med. surg. J.*, **161,** 839.
PHELPS, W. M., and KIPHUTH, R. J. H. (1932) The Diagnosis and Treatment of Postural Defects. Springfield, Ill., and London; p. 161.
ROPER, R. E. (1948) Some Aspects of Physique in Boys and Girls. The Research Board for the Correlation of Medical Science and Physical Education, London.
STEINDLER, A. (1955) Kinesiology. Springfield, Ill.; p. 128.
WESSON, A. S. (1938) *Proc. R. Soc. Med.*, **23,** 273.
WILES, P. (1937) *Lancet*, i, 911.
—— (1949) Essentials of Orthopædics. London; p. 8.

Dr. Wilfred Barlow: *Postural Deformity*

Perhaps the best way to indicate the prevalence of postural deformity will be to give the results of a survey which I have recently carried out at one of our leading Physical Education Colleges, a college where a high physical standard is required at entry, and which draws on some of the best athletes and games players in the country. It can be reasonably

claimed that this group of students have applied themselves from an early age to the development of their bodies, particularly in the gymnasium: and they are destined to become Physical Education teachers all over the country.

The entire group of first and second year students were photographed (Barlow, 1955*a*), using a squared background, and a turntable which revolves into three standard positions. This ensures identical conditions, and the major postural faults show up as clearly as is possible under static conditions.

The faults have been analysed in Table I, giving a rating of 1, 2, or 3 "pluses" according

TABLE I.—PROFORMA USED FOR SCORING POSTURAL FAULTS

Head	Poked, Retracted, Tilted, Pulled down
Shoulders	Raised, Dropped, Rotation, Pulled together
Pelvis	Tilt, Rotation, Forward carriage, Gluteal asymmetry
Spine	Scoliosis, Kyphosis, Lateral curvature or thorax displacement, Lordosis
Stance	Hyperextended knees, Int. rotation knees, Forward inclination, Symmetry
Tension	Specific, General

to the severity of the fault. Many of the faults are reduplicated in the Table—a dropped shoulder is frequently the result of a lateral curvature which also may involve a head twist and a rotation of the pelvis, although each may occur separately. As far as is possible, a fault is only scored once. A given observer soon achieves a uniform pattern of scoring. My average scoring for the first and second year group only varied by 1%, which indicates that the method is accurate.

Analysing faults in this way, one soon finds a definite pattern appearing, of 5 well-defined categories—those scoring 0–3 faults who have excellent posture, those scoring 4–5 who have some slight defect, those between 6 and 9 faults who show moderately severe defects, those between 10 and 14 who show severe defects, and those over 15 who show really gross postural deformities. Fig. 1A shows an analysis of the 112 Physical Education students, and

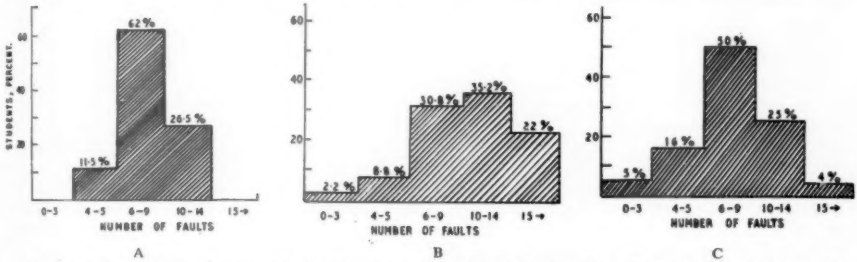


FIG. 1.—Percentage of postural defects in: A, 112 physical education students (females). B, 45 C.S.S. male students. C, 81 female drama students. 0–3 nil; 4–5 slight; 6–9 moderate; 10–14 severe; 15→ very severe.

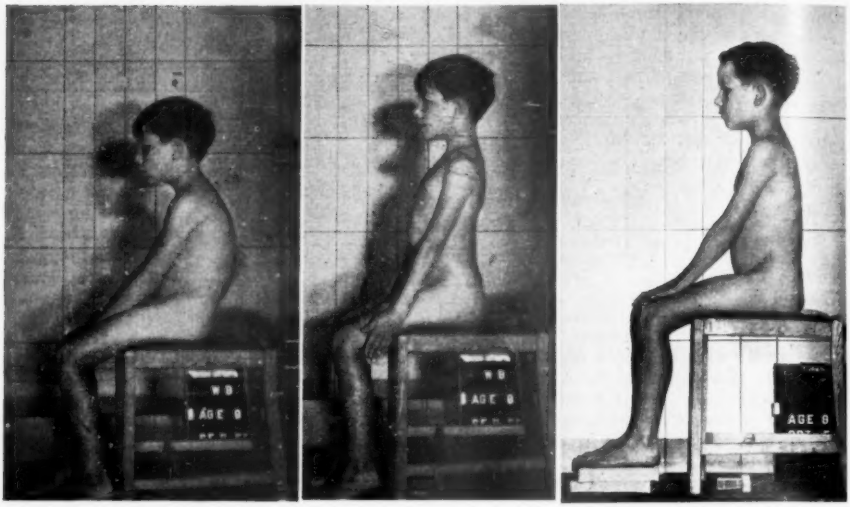
it will be seen that the majority—62%—show a moderately severe defect, 11·5% show a slight defect, and 26·5% show a serious defect. There were no students in the top grade, and none in the lowest grade.

The students from the Physical Training College (Fig. 1A), show a high degree of mesomorphy (muscularity) in their Sheldon physique typing. If we turn to a group of male drama students, in whom the slender physique predominates, we find (Fig. 1B) an average of 11·2 faults: the curve has shifted appreciably to the right. An analysis of 81 female drama students (Fig. 1C) resembles the P.E. group more closely with an average of 8·0 faults, except that there are a few outstandingly good students and a few outstandingly bad ones. Since our purpose is to evaluate methods of educating posture, it is reasonable to begin by establishing the point that whatever methods are being used in our schools, the end-result even in the best students is not good.

Methods of Postural Re-education

The idea that a healthy natural outdoor life, with plenty of good food and exercise, will ensure a reasonably good posture is not always true in my own experience, and we have seen how high is the incidence of defects in P.E. students. However, even if it were true, our main problem would still be how to establish a posture which will stand up to the strain of living in a civilization in which the healthy life may not be easily available.

There is much evidence to indicate that the methods of postural education and re-education employed in the past have not proved successful, and this in my view has been due to an over-



A B C

FIG. 2.—Child sitting (A) slumping, (B) straining to sit up straight, (C) in relaxed position after training.

simplification of the problem. The cause of the problem of postural control is the subject's *postural awareness*, and, at a different level, the *postural model* or *body schema* which the subject uses as a standard against which to detect his postural errors. In the past, too much reliance has been placed on verbal or pictorial instruction to re-educate the postural model, whilst the actual postural ability and its associated awareness has been tackled by exercises. Optimistically it has been hoped that people can "do what they are told", and that a little more will-power and "trying" is all that is required. Fig. 2A shows a small boy with a bad habitual slump; Fig. 2B shows the typical strained effort which most children make when told to "sit up straight"; Fig. 2C shows the improved position which he adopts when his postural awareness has been trained. Words and ideas will only become effective when they are accompanied by demonstration of the sensory experiences to which they refer. Such experience will not be given by an "exercise", as at present understood, but will only be learned after a period of conditioning in which the new model (verbal or otherwise) is associated with the appropriate degree of muscle tension, not only at rest but in preparation for movement, during movement, and after movement. In this way the subject learns a basic resting state of postural equilibrium which he can employ at will. I have elsewhere outlined such a method of re-educating posture by a conditioning procedure (Barlow, 1955*b*), and this method was employed in the following experiment.

Comparison of Methods of Re-education

For the past three years a survey has been carried out at the Central School of Speech in order to assess the efficacy of their methods of postural re-education. As a control group, I have submitted a similar group of students from the Royal College of Music to the conditioning procedure in which a new postural model is linked to the correct experience of postural awareness. The Central School is a training College for speech therapists, speech teachers, and drama students, and is a good group to study since posture is considered by this school to be of fundamental importance throughout the whole three years' training. The Principal had been dissatisfied with their results for some time, and she agreed that it was important for us to find out whether in fact their methods were being effective. One could sum up the methods employed at this school as being based on the giving of verbal instruction and occasional manual adjustment so that the pupil would attempt to do the right thing to correct the posture when a teacher noticed it was wrong. Thus if a shoulder was dropped, the student would be told to correct it by holding it up, and might receive exercises to strengthen the dropped side: if the head was pulled back, the student was told to put it forward, and so on. No attempt was made at a conditioning procedure, and it was taken for granted that if a fault was pointed out and perhaps manually corrected, the student would then be able to maintain the correction. To promote general awareness of posture and movement, great use was made of a form of exercise introduced by Laban, known as

"The Art of Movement", a method much advocated at the recent Ling Conference on School Gymnastics.

In spite of this constant preoccupation with posture at the Central School, the average number of faults in 25 girls at the start of training was 7·5: at the end of training it was 7·9. The average number of faults in 19 men at the start was 10·6: at the end 11·7. In fact deterioration had taken place.

For comparison, the group of students from the Royal College of Music were trained by a conditioning procedure. In this group, the average number of faults in 13 men before re-education was 11; at the end 5. In 17 girls, the average number of faults was 9 before training; at the end it was 4. This represents a considerable improvement. A detailed comparison of the Central School and Royal College students is shown in Fig. 3A (female) and Fig. 3B (male).

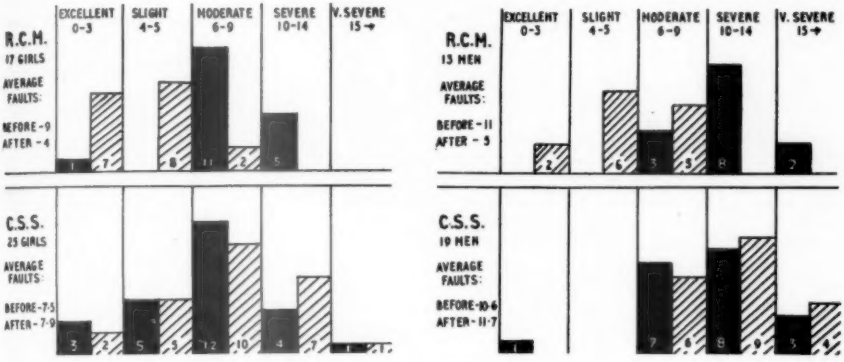


FIG. 3.—Comparison of re-educational methods. Improvement in R.C.M. students, deterioration in C.S.S. students (A) female, (B) male. Black blocks=numbers before. Striped blocks=numbers after training.

This experiment makes it clear that postural re-education will be ineffective unless a new "body schema" is taught, by associating the postural model with an improved postural awareness.

Physiotherapeutic Methods

Turning to a consideration of methods at present used by many Physical Medicine Departments, we should mention only to condemn the use of spinal supports where there is no gross pathology to justify their use. Perhaps the commonest method used by physiotherapists is a combination of exercise and "static holding" (Prosser, 1948).

"In treating the patient with a postural defect, static holdings are carefully taught and the patient encouraged to feel the sense of the good posture. It is this form of muscle contraction which is said to re-educate the postural reflex. By repeated and concentrated holdings, an appreciation of the new posture is established."

This quotation from a physiotherapy textbook is a typical example of current methods. Such methods must be considered from the point of view of whether they increase postural awareness. I have suggested previously (Barlow, 1954) that the muscle spindle mechanism, which mediates much of our postural sense, is put out of action by excessive muscular contraction. It is always hazardous to transfer the results of animal physiology to the human, but there seems to be fairly clear agreement now that postural feed-back from the muscle is more effective when a muscle lengthens than when it shortens; it is difficult to see how the "holding" and over-contraction of muscle can help to promote postural awareness. Moreover, the connexion between excessive muscular contraction and states of anxiety, in which the excessive contraction produces a lack of awareness of the body, is well established. I think it can be reasonably stated that the teaching of muscular contraction as a form of postural re-education to patients who already exhibit muscular over-contraction and an inability to return to a resting state of equilibrium after activity, will only accentuate the problem and will decrease the patient's awareness of what he is doing. Fig. 4 shows a young acrobatic dancer who had received a long course of postural re-education in a physical medicine department.

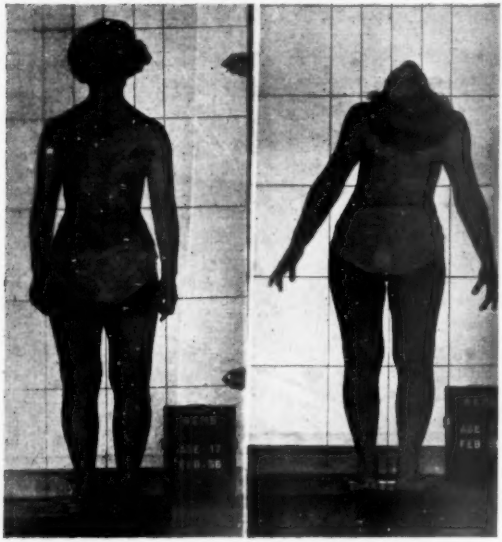


FIG. 4.—Lateral curvature accentuated during extension exercise.

It will be seen that she has a slight lateral curvature and this had caused her pain and prevented her from working. (In passing, it should be noted that postural deformities may be painless provided that stress activities are avoided; but this involves an increasing limitation of the individual's sphere of activity.) In spite of her re-education, this patient was still in pain, and it will be seen that when she does a back-bend, her deformity *increases* considerably. She was quite unaware of this deformity, in spite of her period of re-education by static holding and contraction exercises.

It might be said that these contraction exercises "strengthen the back muscles", but this is based on a faulty conception of "strength". Inman (1952) has shown that the *longer* the resting length of a muscle, the greater the force exerted and the less the electromyographic activity which accompanies it. The "strength" to maintain adequate postural relationships at rest and during movement does not come from muscle-shortening and over-contraction, but from maintaining a correct equilibrium between the various parts of the body. To attain this equilibrium, the patient needs to be taught to release superfluous muscular tension and return to a resting state in which the muscles are lengthening.

CONCLUSION

Here are a few observations on posture work. Firstly, as regards the utilization of conditioning procedures such as I have suggested. The problem here is one of training suitable personnel; once the trained personnel are available, the actual task of re-education need take no longer than is spent on present methods, although it necessarily involves individual as opposed to group instruction.

Secondly, I should like to define the word "Posture" as "A person's willingness and ability to maintain that relationship of the different parts of his body which ensures their most efficient behavioural function and physiological functioning both now and in the future". Such a definition underlines the fact that Posture is a psychosomatic affair, in which habit plays a part, and that "good posture" does not imply some ideal standard, but rather a person's willingness and ability to maintain the best relationship possible for *him*, whether or not there may be some pathology present. The psychosomatic basis of postural deformity becomes apparent to anyone who works for long in this field, for as we proceed with our training, we encounter definite psychological obstacles—habits, attitudes and dispositions to which the patient is profoundly attached and which he is reluctant to change. I have mentioned these problems before (1955*a*). One soon finds that postural awareness occupies a key position in determining a person's idea of himself, and that as this awareness alters, profound alterations may take place in habits of thought.

Our present knowledge of postural control is in its infancy. The crude categories which we employ at present need considerable clarification. I hope that our specialty will be the one which sees the importance of fostering such inquiries.

Acknowledgments.—I am grateful to Sir George Dyson and Miss Gwynneth Thurburn, O.B.E., for permitting students from the Royal College of Music and The Central School of Speech and Drama to volunteer for this study.

REFERENCES

BARLOW, W. (1954) *Ann. phys. Med.*, **2**, 113.
—— (1955*a*) In: Modern Trends in Psychosomatic Medicine. Ed. D. F. O'Neill. London; p. 285.
—— (1955*b*) *Lancet*, ii, 659.
INMAN, V. (1952) *Electroenceph. clin. Neurophysiol.*, **4**, 192.
PROSSER, E. M. (1948) Manual of Massage and Movements. London.

Section of Ophthalmology

President—R. C. DAVENPORT, F.R.C.S.

[*June* 14, 1956]

Some Ocular Effects of Diencephalic Stimulation in the Experimental Animal[1]

By J. GLOSTER, M.D., B.Chir., D.O.M.S., and D. P. GREAVES, F.R.C.S., D.O.M.S.
Institute of Ophthalmology, London

CENTRAL nervous mechanisms have been considered of importance in the regulation of numerous bodily functions, and in the maintenance of the steady state of the internal environment. In particular, much attention has been paid to the diencephalon from clinical, anatomical and physiological aspects.

From the experimental standpoint it has been shown (Bard, 1928 ; Ranson and Magoun, 1933) that when structures within the posterior part of the hypothalamus are stimulated marked activity of the sympathetic nervous system results. These responses, found in such emergency states as fear and anger, are accompanied by vasoconstriction in the skin and gut, an increase in heart rate, contraction of the spleen, dilatation of the pupil and contraction of the nictitating membrane in animals which possess one.

In view of this influence, exerted on many viscera, is it likely that the eye is in any way specifically affected and does its clinical application extend to glaucoma? The idea that the diencephalon influences the intra-ocular pressure is not new and much speculation has been based on physiological and, in particular, clinical features. We are familiar with cases which suggest some such connexion; for instance glaucoma patients who produce a sudden rise in intra-ocular pressure as a result of an emotional disturbance, and the effect of barbiturates in lowering the tension or preventing the rise in similar cases is well known. In fact, certain authors, notably Magitot (1949), Elwyn (1938) and Thiel (1952), have postulated the existence of "centres" controlling ocular tension and are confident that they will be revealed by future work.

Present ideas on the association between the higher vegetative systems and the eye are based therefore more on speculation than physiological facts, and there is thus need for further experimental study. Our aim, therefore, is primarily a physiological one, the intention being to examine in more detail the responses in the eye to stimulation in an area which is known to produce autonomic responses.

Previous work on diencephalic stimulation dates back to Karplus and Kreidl (1909) who found that electrical stimulation of the antero-lateral hypothalamus resulted in sympathetic responses, and later they showed that these responses could be elicited even when the cerebral hemispheres had been removed sufficiently long before to allow degeneration of cortico-fugal fibres. Thus the idea was conceived that the hypothalamus contained "centres", and the theory of the presence of an integrative vasomotor centre was furthered by the reports of Magoun (1938) and Eliasson *et al.* (1954).

From a functional standpoint stimulation of the posterior part of the hypothalamus is known to be accompanied by sympathetic activity whilst stimulation in the middle and anterior parts is thought to evoke parasympathetic responses. This division is far from being clear cut; for example, pressor and depressor responses have been reported from the same area, whilst yet again similar responses have been obtained from stimulation of widely scattered points.

As far as structure is concerned the enthusiasm of anatomists has led to descriptions of much detailed cyto-architecture, and as many as 20 nuclear masses are reported in the hypothalamus (Ingram *et al.*, 1932), though no functional correlation to the anatomical detail has been demonstrated.

It is therefore hardly reasonable to expect that any nervous control of the intra-ocular pressure should be mediated by a discrete anatomical structure. For the present we would prefer not to impose any rigid anatomical limits upon a regulatory mechanism, if such exists.

[1]For publication the original paper has been shortened and much detail has of necessity been omitted, particularly regarding methods. This detail will be supplied in the publication of subsequent work.

Previous Work

Earlier work on the eye reactions was confined mainly to pupillary responses as incidental to more general effects. The work of Ranson and Magoun (1933) showed that pupillary dilatation could be obtained from almost anywhere in the hypothalamus but mainly from the lateral hypothalamic area, the region around the fornix and throughout the length of the hypothalamus. Hess (1939) showed that stimulation of the anterior and medial parts of the hypothalamus was accompanied by a fall of blood pressure and contraction of the pupil, the opposite effects being obtained when the posterior and lateral areas were stimulated.

Only recently has more specific attention been paid to the influence of the hypothalamus on intra-ocular pressure, for example by Schmerl and Steinberg (1950), Nagai *et al.* (1951), Weinstein (1954) and still more recently by von Sallmann and Loewenstein (1955). The last-mentioned approached the problem more critically and employed a better technique, although the area investigated was comparatively limited especially in the parasagittal direction. Their factual account of the results indicates the intricate nature of the matter. In general, stimulation of a ventral zone in the hypothalamus led to a mass sympathetic discharge accompanied by rises of blood pressure and intra-ocular pressure. From a more dorsal region they obtained changes in intra-ocular pressure which were isolated events bearing no constant relationship to blood pressure changes.

Our own experiments are similar in principle to those of previous investigators, but we felt that there was a need to use a standard stimulus throughout the series of animals in order that a fair comparison could be made between the observed effects. We have also extended the investigation into more lateral areas of the diencephalon.

Methods

Cats weighing approximately 3 kg. were anæsthetized with intravenous chloralose (1% solution, 100 mg./kg.). For each experiment the head of the cat was fixed in a stereotaxic instrument and a dental drill employed for drilling holes in the skull in the appropriate position. Points within the brain were referred to the usual stereotaxic planes, our zero H level being the horizontal plane passing through the internal auditory meatuses and the lower orbital margins.

The femoral arterial blood pressure and intra-ocular pressures were continuously recorded photographically with the aid of optical manometers (*see* Greaves and Perkins, 1952). Movements of the nictitating membranes were recorded on the same record by means of a mirror fixed to a lever attached to the nictitating membranes.

Changes in pupil size were measured and correlated with blood pressure and intra-ocular pressure changes in the final assessment of the results of the experiment.

Stimulation

For this particular series of experiments we employed unipolar cathodal stimulation, the anode being placed within the rectum. The electrode itself was of 4/1,000 inch diameter nickel wire within a 0·8 mm. external diameter straight glass capillary tube, the whole mounted in a watchmaker's lathe chuck, and capable of being moved in three planes at right angles. A square wave pulse of 1 msec duration, 30 c/s was used, the circuit being arranged to give a current of 0·2 mA and to avoid variations due to polarization at the electrode tip. This stimulus was chosen by trial and error in preliminary experiments as being the lowest intensity causing full dilatation of the pupil in a suitable area. The electrode was placed in position at H+15 and after three minutes the first stimulus was applied for 60 seconds. Subsequent stimulations of 60 seconds duration were made at 5-minute intervals, the electrode being lowered 1 mm. between stimulations, each point in the brain receiving only one application of the stimulus. Two electrode tracks were made on each animal, one on each side of the mid-line, and generally separated by 7 mm. The position of the electrode was determined by subsequent histological examination of the brain, allowance being made for shrinkage of the tissue during fixation.

Diagrams modified from the Atlas of Jasper and Ajmone-Marsan were prepared for frontal planes separated by 1 mm. extending from A 9 to A 14 and the results of each experiment were plotted on these. After examination of the slide showing the needle tip it was possible to decide upon the appropriate frontal plane diagram to be used. The lateral points were decided by the relationship of the needle tracks to the anatomical structures seen on the slide.

Results

These results were obtained in 32 experiments in which 630 points in the diencephalon were stimulated. Only the main features can be given here. These will be reported under four headings, viz. (1) Pupillary responses; (2) Nictitating membrane effects; (3) Blood pressure effects, and (4) Intra-ocular pressure changes.

Pupillary Responses

Pupillary dilatations were elicited by stimulation of points which were scattered widely throughout the diencephalon, but the most marked effects were obtained from stimulation in the lateral part of the hypothalamus. The dilatations were usually bilateral and approximately equal on the two sides. The impression was gained that dilatations obtained from stimulation in the hypothalamus differed in some respects from those arising from stimulations elsewhere. Dilatations from stimuli in the thalamus were small (usually 1–2 mm.) and took place slowly. Dilatations from stimuli in the hypothalamus were larger and the pupil began to dilate rapidly as soon as the stimulus was switched on, reaching a maximum in 5–10 seconds. The pupil began to return to its initial size as soon as the stimulus was switched off.

Fig. 1 shows the pupil effects from stimulation of points in the diencephalon in the frontal plane A 12.

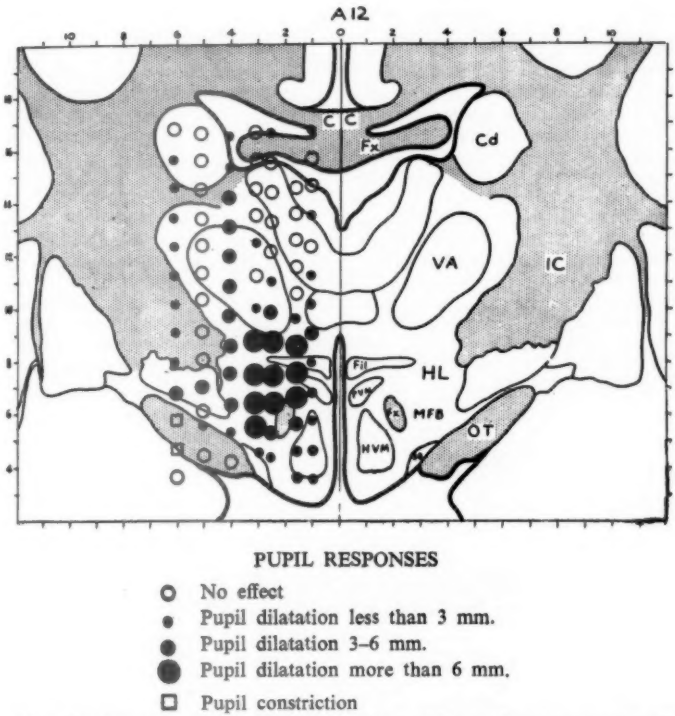


FIG. 1.—Map showing points in the diencephalon from which pupillary responses were obtained. Frontal plane 12 mm. anterior to inter-aural line. The edges of the map are marked in divisions representing millimetres of brain tissue. The vertical scale zero is the horizontal (H) plane.

Contractions of the pupil were seldom elicited in these experiments, but two points in the optic tract from which small pupillary contractions were obtained can be seen in Fig. 1. Contractions were also obtained from points in plane A 8 which lies slightly posterior to the area in which we were mainly interested.

Nictitating Membrane Effects

Whereas pupillary responses were often observed, nictitating membrane effects were relatively uncommon and the changes were always small. Both contractions and relaxations of the membrane were recorded, but contractions occurred about twice as frequently as relaxations. It should be added that some changes in the nictitating membrane record must be interpreted with caution since they may be due to small movements of the rectus or orbicularis muscles.

Blood Pressure Responses

Alterations in the systemic blood pressure often induce changes in intra-ocular pressure in experimental animals and therefore a brief description will be given of the blood pressure changes observed in this investigation.

The most frequent blood pressure change was a simple rise or fall during stimulation, but complex effects also occurred. The response usually started promptly at the commencement of stimulation, and sometimes persisted for a time after the stimulus was switched off or was succeeded occasionally by a temporary change in the opposite direction.

Blood pressure effects were obtained from stimulation of many areas in the diencephalon but the most marked effects were elicited from the hypothalamus, where rises of blood pressure were obtained more frequently than falls.

Some correlation could be established between the type of blood pressure response and the site of stimulation, but this was not as consistent as the analogous correlation for the pupillary effects. This suggests that the pupillary response to hypothalamic stimulation is determined by a smaller number of factors than the blood pressure response.

Intra-ocular Pressure Effects

Since alterations in blood pressure frequently influence intra-ocular pressure, it is of comparatively little value to study the intra-ocular pressure changes without taking into account simultaneous blood pressure effects. If biphasic responses are excluded, there are nine possible combinations of intra-ocular pressure change and blood pressure change. When the results of 630 stimulations were analysed on the basis of this classification, the main conclusions were: (i) in slightly more than half the stimulations there was no change of intra-ocular pressure, (ii) the majority of intra-ocular pressure changes were accompanied by blood pressure changes in the same direction, (iii) changes of intra-ocular pressure which were independent of blood pressure changes resulted from slightly less than one-fifth of all stimuli, and (iv) the incidence of each combination of intra-ocular pressure and blood pressure was essentially the same in the two eyes and independent of the side of stimulation.

The most interesting intra-ocular pressure responses were those which could not be explained by simultaneous blood pressure changes, and two types of response requiring further consideration are: (1) a rise of intra-ocular pressure unaccompanied by a rise of blood pressure (Fig. 2), and (2) a fall of intra-ocular pressure accompanied by a rise of blood pressure (Fig. 3).

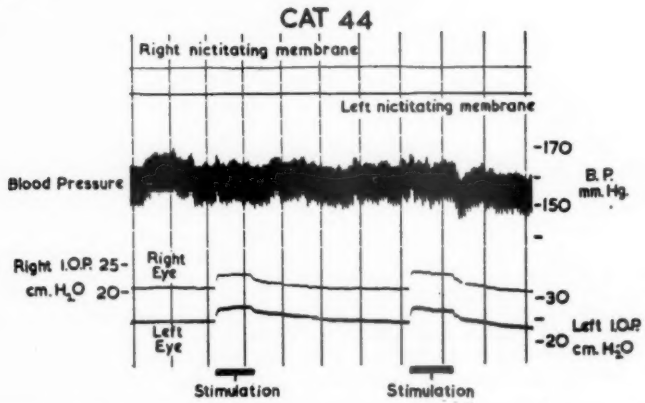


FIG. 2.—Tracing showing bilateral rises of intra-ocular pressure unaccompanied by blood pressure changes. (Interval between vertical time-marker lines=60 sec.)

With regard to the first of these, there are two observations which may explain how this rise of intra-ocular pressure occurs in the absence of a rise of blood pressure. Firstly, at times the rise in pressure and the subsequent return at the end of stimulation were rapid, and, secondly, they were occasionally accompanied by abrupt movements of the nictitating membrane record. These two observations suggest that the increase in intra-ocular pressure is sometimes due to pressure on the globe from contraction of striated or unstriated muscle within the orbit.

The combination of a fall in intra-ocular pressure with an increase in systemic blood pressure could be explained in several ways, but the fall in intra-ocular pressure resembles the effect of stimulation of the cervical sympathetic trunk. Therefore it is possible that, in the area of the hypothalamus yielding this response, stimulation evokes a sympathetic discharge which produces a rise of general blood pressure together with a marked vaso-constriction in a vascular territory which includes the eye. However, further experiments are needed to establish this hypothesis.

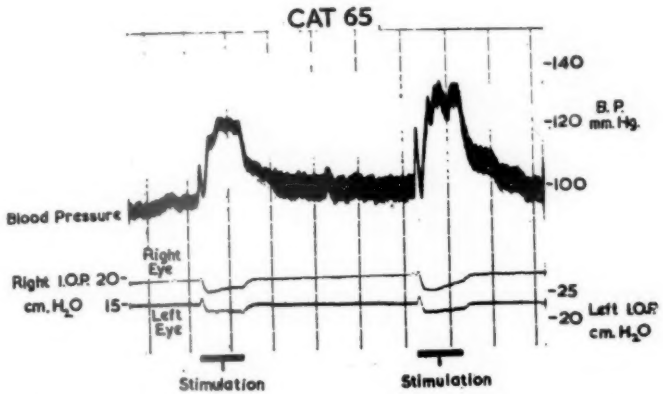


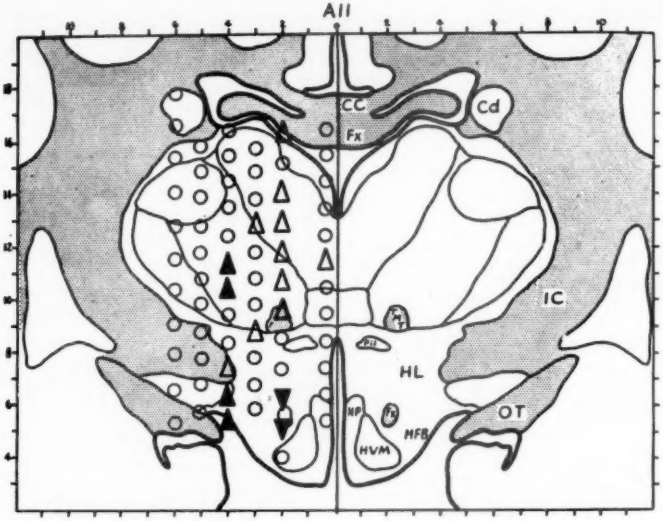
FIG. 3.—Tracing showing bilateral reduction of intra-ocular pressure accompanied by rise of blood pressure. (Interval between vertical time-marker lines = 60 sec.)

An attempt has been made to correlate the intra-ocular pressure responses which were independent of blood pressure changes with the site of stimulation in the diencephalon. The results for one frontal plane (A 11) are illustrated in Fig. 4. Intra-ocular pressure rises which were not associated with rises in blood pressure were elicited from points which, although widespread, occurred most frequently in the postero-dorsal region of the diencephalon. The points at which stimulation gave a fall of intra-ocular pressure with a simultaneous blood pressure rise were few in number, but, with one exception, were confined to the medial part of the hypothalamus and were grouped round the fornix. As far as can be judged from the present results, it appears that stimulation in this area elicits this type of response fairly consistently.

Comment.—The pupillary responses reported here do not differ substantially from those described by previous workers (e.g. Ranson and Magoun, 1933). Pupillary contractions were seldom elicited, but this is probably due in part to the use of chloralose anæsthesia which produced slit-like pupils in most of the cats.

The most interesting responses were those in which the intra-ocular pressure fell although accompanied by a rise in general blood pressure. The interest is heightened by the fact that they appear to be elicited from a comparatively well-defined area of the hypothalamus closely related to the anterior column of the fornix. It seems likely that the reduction of intra-ocular pressure is due to constriction of the ocular blood supply, but it is not yet clear whether this vasoconstriction is confined to the eye or is more generalized, involving perhaps the entire head region.

Our observations that diencephalic stimulation can cause changes of intra-ocular pressure which are not merely reflections of blood pressure variations suggest that efferent pathways may exist by which the central nervous system could influence the intra-ocular pressure. Nevertheless proof of the existence of such pathways would strengthen, but not establish, the concept of a nervous mechanism controlling the intra-ocular pressure, since it must be borne in mind that such a mechanism would require an afferent pathway for which there is at present no definite evidence. Finally, we must emphasize that our observations do not necessarily indicate that the diencephalon itself influences the intra-ocular pressure, since the responses obtained could have arisen from the stimulation of tracts which run through the diencephalon without interruption or which are relayed there. Thus, while the observations



INTRA-OCULAR PRESSURE RESPONSES

Δ I.O.P. rise with no change of B.P.

▲ I.O.P. rise with B.P. fall

▼ I.O.P. fall with B.P. rise

O Other types of response

FIG. 4.—Map showing points in the diencephalon from which independent changes in intra-ocular pressure were elicited. Frontal plane 11 mm. anterior to inter-aural line.

which have been described provide a useful basis for further work, it may be necessary to extend the search beyond the diencephalon into other parts of the central nervous system.

Acknowledgments.—We are grateful to Sir Stewart Duke-Elder for his encouragement in this research and also for the help given by the Department of Medical Illustration. We should also like to acknowledge a grant from the Pigott Wernher Trust Fund covering the expenses of this work.

REFERENCES

BARD, P. (1928) *Amer. J. Physiol.*, **84**, 490.
ELIASSON, S., LINDGREN, P., and UVNAS, B. (1954) *Acta physiol. scand.*, **31**, 290.
ELWYN, H. (1938) *Arch. Ophthal., Chicago*, **19**, 986.
GREAVES, D. P., and PERKINS, E. S. (1952) *Brit. J. Ophthal.*, **36**, 258.
HESS, W. R. (1939) *Klin. Mbl. Augenheilk.*, **103**, 407.
INGRAM, W. R., HANNET, F. I., and RANSON, S. W. (1932) *J. comp. Neurol.*, **55**, 333.
JASPER, H. H., and AJMONE-MARSAN, C. Stereotaxic Atlas of the Diencephalon of the Cat. Nat. Res. Counc., Ottawa, Canada.
KARPLUS, I. P., and KREIDL, A. (1909) *Pflüg. Arch. ges. Physiol.*, **192**, 138.
MAGITOT, A. (1949) *Ann. Oculist., Paris*, **182**, 569.
MAGOUN, H. W. (1938) *Amer. J. Physiol.*, **122**, 530.
NAGAI, M., BAN, T., and KUROTSU, T. (1951) *Med. J. Osaka Univ.*, **2**, 433.
RANSON, S. W., and MAGOUN, H. W. (1933) *Arch. Neurol. Psychiat., Chicago*, **29**, 1179.
SCHMERL, E., and STEINBERG, B. (1950) *Amer. J. Ophthal.*, **33**, 1379.
THIEL, R. (1952) *Ophthalmologica, Basel*, **123**, 195.
VON SALLMANN, L., and LOEWENSTEIN, O. (1955) *Amer. J. Ophthal.*, **39**, 11.
WEINSTEIN, P. (1954) *Ophthalmologica, Basel*, **127**, 164.

BOOK REVIEWS

Selection of Anæsthesia. The Physiological and Pharmacological Basis. By John Adriani, M.D. (Pp. xvii + 327; illustrated. 47s. 6d.) Oxford: Blackwell Scientific Publications. (Springfield, Ill., Charles C. Thomas.) 1955.

The preface to this work states: "This book is not for those interested in administering anæsthetics. It is for individuals who wish to become familiar with the principles and methods of anæsthesiology, for physicians who evaluate operative risks . . . who are responsible for prescribing anæsthetic drugs . . . but do not themselves administer anæsthetics. . . . The fundamental principles presented, though elementary, may also be of interest to physicians and nurses commencing their training in anæsthesiology . . . and parts may be of interest to medical students."

The author considers how both the type and site of operation, and the presence of intercurrent disease, may influence the choice of anæsthetic method, and he discusses the pharmacology of anæsthetic drugs at length; but—in spite of the book's sub-title—he devotes relatively little space to physiology.

Dr. Adriani appears surprisingly out of sympathy with the use of muscle relaxants, and his failure to stress the importance of maintaining an adequate respiratory exchange when these drugs are used must be strongly criticized. Although he briefly discusses some of the physiological principles involved in the use of controlled respiration, he fails to make clear the importance and wide applicability of this technique to anæsthesia—especially for thoracic surgery. Indeed, many anæsthetists to-day would consider that the virtues of the nitrous oxide-relaxant-controlled respiration technique are such as to render not a few of the author's recommendations out of date.

It will be seen that, though not unsuccessful in its purpose, this book will have little appeal in this country, or in the increasing number of places throughout the world where there are specialist physician anæsthetists; for the selection—and safety—of any anæsthetic depends, above all else, on the skill and experience of the person who is to administer it.

Bentley and Driver's Text-book of Pharmaceutical Chemistry. Revised by John Edmund Driver, M.A., Ph.D., M.Sc., F.R.I.C. 6th edition. (Pp. viii + 751; illustrated. 55s.) London: Oxford University Press (Cumberlege). 1955.

This textbook, now in its sixth edition, started life some thirty years ago, and Dr. Driver has been solely responsible for it since 1929. It is designed for the use of those studying for the examinations in pharmaceutical chemistry here and in the Commonwealth. The author modestly remarks that "the fact that it has been found of use to a wider circle of practising pharmacists is incidental, though gratifying". Covering as it does the chemistry of substances used in medicine, the book is designed to be used in conjunction with the B.P. It is divided into three sections, one dealing with methods of analysis, the second, inorganic chemistry, while the third gives a systematic account of organic chemistry, emphasizing those substances of pharmaceutical importance, a logical arrangement under the circumstances. The sections are more or less independent of one another, but cross references are to be found where necessary. The general arrangement of the text is systematic to facilitate reference, and unnecessary repetition is avoided. The subject matter has been brought into line with the 1953 B.P. Even the ban on heroin is mentioned; not, however, the Government's later hesitation. Most of the line diagrams are new and the text has been entirely reset after extensive rewriting—one of the penalties when dealing with a subject developing as rapidly as pharmaceutical chemistry. The pharmaceutical student who intelligently masters this work ought to have no worries about his examination. The printing and the format are well up to the standard we expect from the Oxford University Press. This is a useful book and it is not showing any signs of old age.

Clinical Biochemistry. By Abraham Cantarow, M.D., and Max Trumper, Ph.D. 5th edition. (Pp. xxxi + 738; 54 illustrations. 63s.) Philadelphia and London: W. B. Saunders Company. 1955.

This is the fifth edition of a standard American text which first appeared in 1932. That it has survived into a fifth edition is an indication not only of the vitality of the text but of the industry and care of the co-authors. It has once more been brought up to date. The index is extremely detailed, occupying some 14% of the total pagination of the volume. Abnormalities present in any disease mentioned will be found indexed under the disease as well as the abnormality. This has led the authors to drop lists of abnormalities in given

diseases from the text itself. The normal aspects of metabolism and biochemical mechanisms are discussed in considerable detail as a basis for the better understanding of the aberrations of such processes in disease. At the end of each chapter there is a series of references to review articles in English, by far the most of them in American journals. There are no direct references to original articles. This may be an advantage for the student as well as the clinician, as the discussions and descriptions of the findings are so condensed that internal references could be distracting. In the text itself, too, cross referencing to related problems is adequate, and very useful. This type of arrangement is essential to allow for a reasonable condensation of the vast amount of information now available as clinical biochemistry. This means that the text to be used to the best advantage should not be read straight through, but rather taken piecemeal. When methods of determination or assay are mentioned, sufficient information is usually given to form an adequate basis for the assessment of the value of the figures obtained, which after all is what should now be expected in such a textbook. This book should prove a very useful aid in following the biochemical intricacies of disease and facilitate their understanding.

Nursing Care of the Newly Born Infant. By W. S. Craig, B.Sc., M.D., F.R.C.P.Ed., M.R.C.P., F.R.S.E. (Pp. viii + 472; 225 figs. 35s.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

The preface of this book states that it is primarily intended for the midwife and family doctor, and it can certainly be recommended to both. The text is laid out clearly, making it a good quick reference book, but at the same time it is very "readable" for anyone wishing more prolonged study. The opening chapters of statistics and definitions are clear and useful. This is followed by a chapter on normal fœtal development and the causes of fœtal developmental errors. Daily routine care of the newborn follows, and then chapters on natural and artificial feeding. The chapters on minor departures from the normal, trauma and infections are all good.

The outstanding features of this book are the very practical approach to the subject and the excellent illustrations.

Senior pupil-midwives can be recommended to use this publication as a reference book, especially if they are advised that there may be minor differences of treatment from that of their own school. This must be expected in any textbook.

Despite the many good midwifery textbooks, there has long been a need for one which gave more detailed information on the baby. "Nursing Care of the Newly Born Infant" makes a considerable contribution to supplying this need, and can be recommended to hospital libraries and individual practitioners.

Synthetic Drugs. By H. Ronald Fleck, M.Sc., F.R.I.C., F.R.M.S. (Pp. viii + 380. 70s.) London: Cleaver-Hume Press Ltd. 1955.

The author does not attempt to cover the whole field of drug synthesis. He has made a reasonably wide selection, including examples of the more important types and also of a number of substances generally of known constitution not yet readily available to synthetic approach. The various substances are grouped under broad pharmacological activities which on occasion may lead to strange groupings: While colchicine relieves the pain in gout, it is found in the same class as pethidine, and Pavatrine appears among the muscular relaxants such as *d*-tubocurarine. The short semi-historical introductions and pharmacological explanations, while often useful and interesting, suffer at times from their heavy condensation. It is true that Simpson did start using ether in midwifery in 1847, but within less than twelve months he had transferred his allegiance to chloroform. Benadryl is described as the first antihistamine synthesized, and the important early French work does not get adequate credit. The main function of the book is, however, to give an exposé of the various methods of synthesis including wherever necessary, the details of the synthesis of essential intermediates, and a general description of their chemical properties. This description is followed by a short description of the clinical data associated with the use of the drugs. This is a section of varying interest where the complications of modern physiology militate against the simplification the author desired. The definitions of biological units are not always helpful, insulin is not measured in mouse units, and the condensed account of various biological tests suggests he has fortunately not had to wrestle with their practical difficulties and definitions. The formulæ and the syntheses are well set out. The number of errors is not excessive, and most of them can be corrected by reference elsewhere in the text. The author has undertaken a difficult task, but in his main aim he has been successful—the description of the synthetics will be of great use to a wide circle.

Blood Supply and Anatomy of the Upper Abdominal Organs. By Nicholas A. Michels, M.A., D.Sc.(Louvain). (Pp. xiv + 581; 172 illustrations, including 166 in colour. £8.) London: Pitman Medical Publishing Co., Ltd. (Philadelphia: Lippincott.) 1955.

The aim of this volume is to give the surgeon an account of the anatomy and embryology of the upper abdominal organs. As the author states, "Items have been selected and discussed in such a manner as to give the average surgeon a sense of anatomic security when operating". The book is especially concerned with the detailed distribution of the blood supply to the viscera in the upper part of the abdomen. The numerous variations are profusely illustrated in the many excellent drawings which are a special feature of the atlas.

The preparation of the atlas has taken nearly twenty years to complete and has involved the dissection by the author of over 500 subjects. In addition he has examined 150 plaster corrosion casts of human livers made by Healey and Schroy, of the Daniel Baugh Institute of Anatomy.

The volume is a fine record of personal observations, correlating them with the investigations of other workers. The comprehensive review of the earlier literature is especially useful. The information on the Embryology, Topographic Relations and Developmental Anomalies of the organs in the upper part of the abdomen is well arranged and will be a useful source of information to the surgeon who requires a concise statement on these topics. There can be no doubt that in view of the extensive surgery now performed on the organs of the upper part of the abdominal cavity, this book will serve a very definite need.

It is only after going through the book carefully that one comes to appreciate fully the magnitude of the task involved in its compilation. This is a useful work and can be recommended without reservation.

The Cytology and Life-History of Bacteria. By K. A. Bisset, D.Sc. 2nd edition. (Pp. xii + 164; 68 illustrations. 25s.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

In the five years that have passed since the first edition of this work there have been some notable advances in the subject, and considerable attention has been paid to these in the second edition which now consists of 164 as compared with 136 pages. The number of illustrations has increased from 43 to 68. As before, the style is simple and the words used unambiguous and carefully chosen, while the illustrations are again first class. The main criticism of the earlier edition was that many sections contained somewhat dogmatic statements with little reasoned discussion on the evidence for and against their acceptance. This fault is still present, but it would be fair to say that many parts of the subject are dealt with in a more objective way than previously and that more generous recognition has been given to the work of others—notably the interesting work of Tomcsik on differential staining of different cell components by the use of specific antisera. The author himself makes a plea for a more critical attitude towards cytological evidence and wisely condemns the "uncritical reliance of a single worker or a small group upon a single method".

Bacterial cytology no longer moves on purely morphological lines and it is becoming increasingly clear that future advances demand the closest collaboration between cytologists, geneticists, biochemists and others. As Dr. Bisset puts it, "although little has so far been done to correlate genetical and cytological information, a gratifying degree of mutual support has already been observed".

The excellent quality of the figures has already been mentioned, but the (presumably deliberate) lack of reference to them in the text considerably lessens their value, since it is seldom possible to see exactly which appearance is illustrated in which figure. The same criticism applies with equal force to the method of presenting the references. In spite of Dr. Bisset's vigorous defence of the system, it does multiply references unnecessarily, and yet they are seldom to be found in the right place at the right time, at least by someone who is not already familiar with the details of the literature.

Modern Methods of Feeding in Infancy and Childhood. By Donald Paterson, B.A., M.D.Edin., F.R.C.P.Lond., F.R.C.P.Canada, and George H. Newns, M.D.Lond., F.R.C.P. 10th edition. (Pp. 188; illustrated. 15s.) London: Constable & Company Ltd. 1955.

The revised edition of this already popular work will be welcomed by the medical and nursing professions. The section on breast feeding has been elaborated and exceptionally well illustrated, and that on artificial feeding has been brought up to date with particular attention paid to the avoidance of underfeeding. A notable addition is the chapter on

diets for sick children, including amongst others the low-sodium diet in nephritis and the gluten-free diet in cœliac disease, together with recipes using wheat starch. The tables giving the composition of the better known milk foods and cereals should be useful for reference.

Handbook of Toxicology. Vol. 1. Acute Toxicities of Solids, Liquids and Gases to Laboratory Animals. Edited by William S. Spector. (Pp. viii + 408. 49s.) Philadelphia and London: W. B. Saunders Company. 1956.

This is the first of a projected series of at least five volumes, which it is hoped will be published in the next two years. It aims to supply as comprehensive data as are available on the toxicology of chemicals, antibiotics, alkaloids, pesticides, &c. This ambitious programme is being carried out as a combined effort under the ægis of the Wright Air Development Centre of the United States Air Force, the National Research Council's Committee on Toxicology and Dr. W. F. von Oettingen of the National Institutes of Health. This first volume consists of two extensive tables—the first, on the acute toxicities of some 2,120 compounds (solids, liquids and gases) to laboratory animals, and the second gives the lethal concentrations of gases, vapours and fumes in the respired air in laboratory animals, and lists some 243 substances. Such lists are not ordinarily available in laboratory libraries. A certain amount, of course, could be found in Heffter's Handbuch or some parts of Tabulæ Biologicæ, and for general laboratory purposes the Sollman Hanzlik laboratory guide, and for the rat especially the second edition of Farris and Griffith. Then for the years 1941–1946 there are additional data in Anderson, Murayama and Abreu's Pharmacology and Experimental Therapeutics. Otherwise it was only possible to check dosages by reference direct to the original papers. The data are arranged alphabetically, according to the name of the compound. The source of the information is given in every case, and when the original data have allowed statistical treatment, this has been reported. Naturally this does not apply to information on earlier compounds of toxicological interest. In many cases it is surprising how few species may have been tested, but in some cases the reverse also is true. The lay-out of the tables is clear and the print excellent. The editor is to be congratulated on the general format and clarity. The index is adequate and easy to use. The price is reasonable, but the volume will have to be handled with care because of the style of the binding. However, this may be a minor point as the book is a reference book not requiring to be read right through. If the project goes through as planned, the laboratory worker will have at his hand a mass of useful data otherwise difficult to collect. It is a publication that should be in all laboratories, and on the library shelves of those interested in any of the numerous aspects of toxicology.

Studies on Fertility. Including papers read at the Conference of the Society for the Study of Fertility, Birmingham, 1955. Being Volume VII of the Proceedings of the Society. Edited by R. G. Harrison, M.A., D.M. (Pp. x + 156; illustrated. 25s.) Oxford: Blackwell Scientific Publications. 1955.

This book is the seventh annual volume of the Proceedings of the Society for the Study of Fertility, and the second to appear in book form. It consists of 14 separate papers, half of which concern male fertility and half female fertility. The only sex inequality noted, apart from a masculine dominance on the Committee of the Society, is that 3 papers are devoted to fertility of the human female and only 2 to the human male.

In his preface Professor Harrison states that it is the policy of the Society to present recent advances in research on fertility from as wide a field as possible. The 9 papers dealing with fertility in experimental animals may be of interest to zoologists and perhaps to veterinary workers, but have no obvious relationship to human fertility. Indeed it is not clear to the reviewer why it is of any value to know that the rapidity of degeneration following chronic ischæmia in the rat testis is directly proportional to the amount of testosterone injected intraperitoneally.

Turning to the two papers on male fertility: (i) C. W. Taylor and Dorothy Shotton report 2 cases of idiopathic retrograde ejaculation into the bladder, in one of which cervical insemination of the bladder ejaculate was successfully performed; (ii) Clare Harvey reports an interesting study of spermatogenesis in subfertile men.

"Observations on the Post-coital Test" by G. I. M. Swyer is by far the most important paper in this volume as far as the clinical gynæcologist is concerned; it is the result of careful correlation of post-coital tests with seminal analyses in women who did and did not conceive. Although Swyer concludes that the post-coital test has both prognostic and diagnostic value he shows that the quality of cervical mucus has little significance whereas sperm invasion of the mucus is significantly better in those who conceived. The diagnosis of mechanically ineffective coitus can only be made by a post-coital test which shows no sperm in spite of an adequate semen analysis.

Section of Urology

President—DAVID BAND, F.R.C.S.Ed.

[*January* 26, 1956]

DISCUSSION ON URETHRAL INJURIES

Mr. D. S. Poole-Wilson: *The Immediate Treatment of Urethral Injuries.*

In recent years the treatment of injuries of the urethra has tended to become more stereotyped. In civil life the injury is relatively uncommon and few surgeons receive sufficient cases to allow adequate comparison and evaluation of the different modes of treatment. Simpson-Smith (1936) and Silverstone (1942) reviewing the literature found only 16 authors recording a series of 10 or more cases. Many of these series consisted of collected results and therefore did not represent true personal experience. The segregation of traumatic and gun-shot wounds of the urethra into special units during the last war yielded some larger series (Culp, 1947; Lewis, 1944, 1947; Poole-Wilson, 1947 and 1949; Robinson *et al.*, 1946). Clarke and Leadbetter (1952) have compiled a review and bibliography of reported cases. Gordon-Taylor (1950) has edited British Army experience. In civilian life this segregation is now less marked and it again becomes difficult to evaluate treatment. In this country, Bowesman (1950), Fergusson (1949), Rowlands (1953) and Trafford (1955) have recorded series of cases.

Sequelæ of Urethral Injuries

Injuries of the urethra alone should not have a high mortality and when death occurs it is usually the result of severe concomitant injuries or of delayed or inadequate treatment. Stricture formation, urinary fistulæ and chronic urinary infection may, however, be all too frequent distressing sequelæ. Morson (1942) stated "I know of no case where the urethra has been completely torn across, in which the patient has been restored to perfect health". Some stricture formation may be inevitable, but the incidence and severity of these complications may be markedly lessened by good treatment.

Traumatic strictures vary a great deal in their severity and speed of formation. When the urethral injury is severe or secondary infection present a stricture may develop extremely rapidly. If the initial lesion is slight the stricture may only become apparent in the course of many years. The severe strictures may be extensive and tortuous and the urethra surrounded by considerable peri-urethral fibrosis. These factors may render dilatation difficult and a frequent necessity. The accompanying difficulty with micturition is the main factor in maintaining chronic urinary infection.

The Cause of Stricture Formation

Wounds of the urethra unite by the formation of scar tissue and it must therefore be accepted that after any urethral injury some degree of stricture formation is inevitable. Boeckel (1898) wrote "Toute rupture de l'urèthre est un rétrécissement en germe". Treatment must aim to reduce this fibrosis to a minimum. Careful treatment may achieve much; careless treatment may grossly increase the deformity. Success may only be claimed when the urethra finally remains of almost normal calibre, when no fistulæ are present and the urine remains free from infection.

There are four main causes of increased fibrosis at the point of repair:

(1) Inadequate approximation of the severed urethral ends. This leads to the formation of an unnecessary amount of scar tissue. Excision of stricture of the urethra is most successful when the urethral ends are approximated accurately and without tension.

(2) Sepsis at the site of the injury. Sepsis may ruin the most meticulous repair and cause gross scar formation. The sepsis may be introduced by careless initial catheterization or the inadequate care of perineal wounds. The presence of an in-dwelling catheter and urine flowing over the rupture encourage the onset of infection and aggravate it when it occurs.

(3) The severity of the primary lesion. Considerable necrosis may occur in the lacerated urethral tissues and give rise to subsequent fibrosis. The very rapid stricture formation, which may even occur in some cases of incomplete rupture, may be explained on this basis. As long ago as 1906 Pasteau and Iselin pointed out the difficulty of determining the limits of tissue necrosis prior to carrying out an end-to-end suture. Kidd (1921) wrote that it is not the type of operation on the perineum, nor is it the tied-in catheter that is the real or chief cause of subsequent stricture but the pulping and lacerations of the corpus spongiosum. The severity of the stricture is determined by the violence of the blow and can be little influenced by the type of operation performed subsequently. The operator who makes a careful estimate of the amount of damaged tissue and who removes this before suture is likely to get the best results. Nevertheless, he can also improve his results by instituting bladder drainage, by refusing to employ the tied-in catheter, by leaving the repaired urethra entirely alone for fourteen days after operation and then by inspecting the site of repair with the urethroscope before instituting treatment with dilators.

(4) Damage by injudicious dilatation. The healing urethra may be further damaged by dilatation carried out too frequently and with unnecessarily large bougies.

The Principles of Treatment

Consideration of these causes of stricture formation, which have been brought to notice by the pioneer work and observations of Guyon in 1902, Rutherford in 1904, Heitz-Boyer in 1909, Marion in 1912, Kidd in 1921, Turner in 1923, Simpson-Smith in 1936 and others have led many surgeons to adopt the following general principles of treatment:

(1) Urine must be diverted from the damaged urethra until healing is complete.
(2) The torn ends of the urethra must be brought into good apposition.
(3) The use of an in-dwelling urethral catheter must be avoided whenever possible during the process of healing.
(4) Sepsis must be avoided.
(5) Subsequent dilatation must not cause further damage to the urethra.

Classification of Injuries

I. Ruptures
  (*a*) Extrapelvic
    Penile urethra
    Bulbous urethra.
  (*b*) Intrapelvic rupture
    Posterior urethra.
II. External penetrating injuries.
III. Intra-urethral injuries.

Rupture of the urethra occurs when it is damaged as the result of external trauma but without the presence of an open wound. The rupture is said to be complete when the urethra is totally severed and incomplete when only a portion of the circumference is sectioned. The anterior urethra may, however, be contused and the external fibrous sheath, the cavernous tissue or mucous membrane damaged without a rupture occurring through the full thickness of the wall. French authors style these latter injuries respectively as partial external, partial interstitial and partial internal ruptures.

I. Ruptures

Rupture of the Bulbous Urethra

Injury to the bulbous urethra is caused by either a fall astride a heavy object or a kick or blow in the perineum. The urethra is damaged by being crushed against the lower margin of the pubic arch or more rarely the bulb may be sheared off the lower surface of the pelvic diaphragm. When the injury is due to crushing against the pubis the lesion is usually placed about one inch anterior to the point where the urethra perforates the pelvic diaphragm. The lesion may be a contusion, an incomplete or complete rupture.

It is now rare to see extravasation following a rupture of the bulbous urethra. Following a complete or incomplete lesion the internal and external sphincters of the bladder go into spasm and the patient is quite unable to pass urine. It is only when the bladder, if unrelieved, finally overflows that extravasation occurs. Treatment has usually been sought long before this critical period.

When exposed at operation the corpus spongiosum and urethral mucosa may show considerable laceration and bruising rendering it difficult to determine the limits of viable tissue. The divided ends of a complete rupture may appear retracted by as much as one inch. This retraction is largely due to the lithotomy position and the repair is made much easier if excessive hyperflexion of the hips is avoided.

The differential diagnosis of rupture and contusion of the urethra.—In a typical case of rupture of the bulbous urethra there is a history of a perineal injury followed by severe localized pain. Bleeding occurs from the external meatus and a hæmatoma forms in the perineum. The patient may experience an intense desire to micturate but is quite unable to do so. The retention is due to spasm of the vesical sphincters and persists until the bladder finally overflows.

If a patient following a perineal injury which has caused urethral bleeding shows no sign of a perineal hæmatoma or swelling and has passed urine, it may be concluded that the urethra has been contused and that neither a complete nor an incomplete rupture is present. Surgical intervention is unnecessary. The patient should be kept under observation and put on urinary antiseptics. As yet I have never seen a patient suffering from a complete or incomplete rupture of the bulbous urethra who was capable of normal micturition, and believe that when post-traumatic urethral bleeding is unaccompanied by a perineal swelling or hæmatoma no harm is done and an operation may frequently be avoided by asking the patient to attempt gentle micturition.

Treatment

Operations for the repair of the ruptured bulbous urethra may be listed approximately in their historical order of introduction[1]:

[1]Further details of these operations may be found in an article by the author on "Treatment of Injuries of the urethra and bladder", British Surgical Progress 1954, London.

Methods of repair without diversion of the urine from the urethra: (1) Healing around an in-dwelling urethral catheter (Cras and Guyon, 1876). (2) Suture of urethra around an in-dwelling catheter (Birkett, 1866; Guyon, 1876). (3) The operation of Pasteau and Iselin (Guyon, 1902).

Methods of repair using suprapubic drainage of the bladder to divert the urine from the urethra: (4) Rutherford's operation (1904). (5) Suture of the urethra over an in-dwelling catheter. (6) Rutherford Morison's operation (1916). (7) Hey Groves' operation. (8) Marion and Heitz-Boyer's operation (1909). (9) Marion's delayed operation (1921).

Recommended Procedure of Repair

In the author's experience the best results are obtained when the principles previously defined are adhered to and the following procedure, which closely resembles the Marion and Heitz-Boyer operation, is recommended:

(1) The urethra is gently catheterized to determine if the rupture is complete or incomplete.

(2) Suprapubic cystostomy is performed to divert the urine from the urethra.

(3) If the rupture is incomplete perineal exploration is not required. The continuity of the urethra is present and it is unlikely that suture of the incomplete tear will improve on natural healing. When a large perineal hæmatoma is present it should be evacuated.

(4) If the rupture appears to be complete the perineum is explored and a repair performed.

Immediate repair of the urethra is usually desirable. If the patient's condition is poor, if the surgeon is inexperienced in urethral repair or lacks adequate facilities for a meticulous operation, the urine may be diverted from the urethra by a suprapubic cystostomy and the urethral repair carried out either in the course of the next few days or even in six to eight weeks when the perineal contusion will have subsided.

The operation is carried out with the patient in a modified Trendelenburg-lithotomy position, which is very similar to that used for synchronous combined excision of the rectum. This position permits the abdomen, external genitalia and perineum to be cleaned and towelled in one step and allows the carrying out of the suprapubic and perineal stages of the operation without any change of position. Excessive flexion of the hips is avoided as it places the perineum under tension and causes wide separation of the tissues and difficulty in suturing.

[The technique of the repair of the urethra and the after-treatment were demonstrated on lantern slides.[1]]

Rupture of the Posterior Urethra

This usually occurs as the result of severe pelvic injuries, in which the stability of the pelvic girdle is destroyed by fractures or dislocations. The urethra is torn during the ensuing distortion and disruption of the pelvic floor. During violent movement complete rupture may occur in the absence of a fracture and is attributed to the momentum of a full bladder shearing itself and its attached prostate off the pelvic diaphragm.

Much confusion exists in the literature regarding the site and type of rupture. Most authors describe the rupture as occurring immediately above the pelvic floor; others, however, maintain that the urethra may be torn in its course through the pelvic diaphragm. At operation accurate observation is often difficult for the floor of the pelvis usually appears contused and covered with blood clot. It is certainly rare for the pelvic diaphragm to be torn completely through. Any tear commonly involves the thin superior fascia and the muscular layer, the strong inferior layer of fascia remaining intact. When the rupture is incomplete there is usually a tear in the anterior wall at the junction of the prostatic and membranous urethra. This tear may result from partial splitting of the pelvic diaphragm during dislocation of the symphysis, from avulsion by the pubo-prostatic ligaments of a portion of the lower anterior wall of the prostatic urethra or from a shearing of the prostate off the pelvic diaphragm, which has just failed to become complete. The urethra may also be pierced by a fragment of fractured pelvis.

Treatment

Patients suffering from rupture of the posterior urethra are usually extremely shocked and may have severe concomitant injuries. It may therefore be difficult to conform to the general principles for the treatment of ruptured urethræ. The prevention or drainage of urinary extravasation by the establishment of suprapubic drainage is of prime importance and must be carried out at the first opportunity. It is also highly desirable to re-establish the continuity of the divided urethra. French surgeons have held the view that in the presence of shock it is inadvisable to undertake immediate repair. A suprapubic cystostomy is performed and six weeks later an attempt is made to reform the urethra. In England and America it is felt imperative to re-establish the continuity of the completely divided posterior

[1]Details of the operation may be found in British Surgical Progress 1954 and in "Operative Surgery" edited by C. G. Rob and Rodney Smith. London. (Shortly to be published.)

urethra as quickly as possible. With modern methods of resuscitation this may usually be done at the time of the initial operation. Under no circumstances should the repair be delayed for more than a few days for without re-alignment of the urethra dense fibrous tissue may fix the prostate in an abnormal position and render effective repair at a later date impossible.

It is also important that any distortion of the pelvic girdle should be corrected so that the soft tissues of the pelvic floor may assume their normal position.

The ruptured urethra is most commonly approached by the suprapubic route and it is difficult, if not impossible, to obtain a really accurate end-to-end suture. In the presence of a severe disruption of the pelvis there is also a considerable danger that pelvic movement may strain or break the suture line. For these reasons a small in-dwelling urethral catheter is placed in position to act as a splint and ensure continuity of the urethra.

[The repair of the posterior urethra by the suprapubic route and the methods of introducing the in-dwelling urethral catheter were illustrated with lantern slides.]

Hugh Young (1926) and his followers have advocated repair by the perineal route. Hunt and Morgan (1942) have described a combined abdominal and perineal approach.

II. Penetrating Injuries of the Urethra

Penetrating injuries are rare in civil life but may result from falls on sharp objects, stabbing and gun-shot wounds. More commonly they occur as the result of the missile injuries of war.

Missile injuries affect all regions of the urethra and are complicated by open wounds, which may be of considerable extent. The penis may be grossly damaged, the scrotum partially torn away or a large perineal skin defect present. The rectum and other abdominal organs are frequently damaged and portions of the pelvic girdle may be shattered. Amongst these gross injuries it is frequently found that the damage to the urethra is less severe than might be expected. Division is usually incomplete. Wounds of the membranous urethra are the most dangerous from the point of view of stricture formation. Complete dislocation of the prostate on the urogenital diaphragm, such as occurs in severe crush injuries of the pelvis, is rare. Prostato-rectal fistulæ may occur as the result of a missile traversing the prostate and rectum. Many of these fistulæ close spontaneously.

Treatment

The urethral damage may be only one of several major injuries. Following resuscitation and an X-ray examination to locate foreign bodies and fractures, the immediate operation involves, in the first place, the inspection and toilet of the superficial wounds. If an intra-peritoneal lesion is suspected the abdomen is opened through a low mid-line incision and any lesions of the intestine are dealt with. The peritoneal surface of the bladder is carefully examined for signs of perforation. When the rectum is damaged or if gross perineal wounds are present a colostomy is preformed. The bladder is next opened and the urethra explored with a small Tieman's catheter passed from the external meatus. Its passage into the bladder indicates that the urethral injury is incomplete and that, apart from a suprapubic cystostomy to divert the urine, no further immediate treatment of the urethra is necessary. If the catheter is obstructed the site of the lesion is determined.

When the injury is in the membranous or prostatic urethra it is important to ensure that alignment of the urethra is restored and maintained by a small in-dwelling catheter used as a urethral splint. Provided the patient's condition is satisfactory this may be carried out immediately. If the patient's condition is poor a suprapubic cystostomy is performed and the re-alignment of the urethra deferred for a few days.

When the injury is situated in the anterior urethra, provided the patient's condition is good and facilities for the operation and after-treatment are adequate, it is reasonable to establish a cystostomy and repair the urethra at the primary operation. When these conditions do not prevail suprapubic drainage to divert the urine from the urethra is established. The repair may then be carried out in a day or two, frequently at the same time as a delayed primary suture of any perineal wounds. On such occasions, if a catheter is first passed it will frequently be found that a lesion, which was originally thought to be complete, is really incomplete and that no further urethral repair is necessary.

When the penis is severely damaged every vestige of viable tissue must be retained as a careful plastic repair frequently results in a remarkably efficient organ.

III. Intra-urethral Injuries

Intra-urethral injuries may be caused by the introduction of foreign bodies by the patient or through surgical instrumentation.

(1) *Foreign bodies.*—Such injuries usually occur amongst mental defectives or prisoners, during bouts of intoxication or in an "accès de folie érotique" (Marion). The foreign

body may be voided but frequently remains impacted in the urethra or passes back into the bladder. When lodged in the anterior urethra it may usually be identified with a urethroscopy and removed with alligator forceps. If situated in the posterior urethra it may be possible to reach it with a pan-endoscope or to dislodge it into the bladder from where it may be picked out with rongeur forceps. Occasionally a foreign body may have to be removed by urethrotomy or cystotomy. The damage to the urethra is usually slight. Unskilful removal of a rough foreign body, such as an impacted calculus, may cause considerable excoriation of the mucosa.

(2) *Instrumental injuries.*—Surgical instrumentation may cause considerable damage to the urethra. In the normal male it is usually attributable to the incorrect selection of type and size of instruments, carelessness or inexperience in their use, or failure to secure complete relaxation of the patient. The most common error is to implant the tip of the instrument in the posterior wall of the bulbous urethra whilst endeavouring to pass a contracted external sphincter. The mucosa may be perforated and a false passage made in the corpus spongiosum. False passages are, however, more commonly made in an attempt to pass a difficult stricture. Enlargement of the prostate may also give rise to trouble, the tip of the instrument being passed into either the posterior or occasionally into the anterior lobe of the prostate. At times the instrument may be driven on through the prostatic tissue and may enter the bladder through a complete false passage. Rarely a metal instrument may be passed either through the bulbous urethra or through the prostate into the rectum.

Damage to the urethra may also be due to the passage of instruments too large for the calibre of the urethra. The urethra cannot be stretched appreciably above its normal size and if this is attempted partial rupture of the wall will occur. In recent years the passage of too large resectoscopes or punches has caused strictures. These most commonly occur at the external meatus or at the peno-scrotal junction. They may form extremely rapidly and be very tight. Before passing such instruments it is well to estimate the size of the urethra with sounds and then to select a suitable size of instrument. To facilitate instrumentation a small external meatus may be enlarged by meatotomy. If the anterior urethra is of small calibre the instrument may be passed by performing a perineal urethrotomy.

Instrumental injuries may cause considerable immediate hæmorrhage, which usually settles down rapidly. The full thickness of the urethral wall is rarely perforated. Apart from urinary antiseptics to control infection no special treatment is required. If retention ensues a catheter may have to be passed. When the instrumentation has been carried out for retention due to an impassable stricture or to prostatic hypertrophy, suprapubic drainage or a prostatectomy may be required. In the event of an instrument having been passed into the rectum it is advisable to perform a temporary suprapubic cystostomy. Neither a local repair nor a colostomy is required. The fistula almost invariably closes spontaneously.

BIBLIOGRAPHY

BOWESMAN, C. (1950) *Irish J. med. Sci.*, **299**, 495.

CLARKE, B. G., and LEADBETTER, W. F. (1952) *J. Urol.*, **67**, 719.

CULP, O. S. (1947) *J. Urol.*, **57**, 1117.

FERGUSSON, J. D. (1949) *Med. Pr.*, **222**, 599.

GORDON-TAYLOR, G. (1950) *Brit. J. Surg.*, War Surgery Suppl. No. 3, 471.

HUNT, A. H., and MORGAN, C. N. (1942) *Lancet*, ii, 330; (1949) i, 601.

KIDD, F. (1921) I *Congr. Soc. int. Urol.*, **1**, 169.

LEWIS, L. G. (1944) *Surg. Clin. N. Amer.*, **24**, 1402; (1947) *J. Urol.*, **57**, 1173.

MARSHALL, D. F. (1946) *J. Urol.*, **55**, 119.

MORSON, C. (1942) *Proc. R. Soc. Med.*, **35**, 287.

POOLE-WILSON, D. S. (1947) *Proc. R. Soc. Med.*, **40**, 798.

—— (1949) *Brit. J. Surg.*, **36**, 364.

—— (1950) *Brit. J. Surg.*, War Surgery Suppl. No. 3, 471.

—— In: Operative Surgery, edited by C. G. Rob and Rodney Smith. London. (Shortly to be published.)

ROBINSON, J. H., CULP, O. S., SUBY, H. I., REISER, C. W., and MULLENIX, R. B. (1946) *J. Urol.*, **56**, 498.

ROWLANDS, B. C. (1953) *Brit. J. Urol.*, **25**, 51.

SILVERSTONE, M. (1942) *Brit. J. Surg.*, **30**, 70.

SIMPSON-SMITH, A. (1936) *Brit. J. Surg.*, **24**, 309.

TRAFFORD, H. S. (1955) *Brit. J. Urol.*, **27**, 165.

YOUNG, H. H. (1926) Practice of Urology. Philadelphia; **2**, 595.

—— (1928) *Trans. Amer. Ass. gen.-urin. Surg.*, **21**, 405.

Mr. Alec W. Badenoch: *The Later Complications of Urethral Injuries.*

The most important sequela of an injury to the urethra is stricture and this seems to occur at one of three situations: (1) at the fossa navicularis, (2) in the bulbous urethra, and (3) at or near the triangular ligament or urogenital diaphragm. The causes and the treatment of these strictures are often quite different.

Stricture following Instrumentation of the Urethra

Narrowing of the canal at the fossa navicularis occurs in a small percentage of cases after instrumentation of the urethra. It is more commonly found when the external meatus is abnormally small prior to any interference, i.e. when the calibre is less than 20 Charrière. A stricture is likely to develop if the opening is overstretched in order to pass a large instrument or when a catheter which fits too tightly has been left in the urethra for drainage, such as after prostatectomy.

It is probable that the development of such a stricture can be prevented if the opening is enlarged by a formal meatotomy rather than by stretching. A patient with this sort of stricture presents with increasing difficulty of micturition, a very narrow stream, and with increased frequency, some four to eight weeks after instrumentation. The urine is always found to be infected and in most cases the lumen of the canal has closed down so much that only a very small bougie can be passed and quite gentle instrumentation causes very considerable pain. The large majority of these cases respond well to treatment. The infection in the urine must be treated and the stricture dilated once weekly. The lumen of the canal is usually restored to its previous size after a few dilatations.

Traumatic stricture arising elsewhere in the urethra is an entirely different problem. It may form after the passage of an instrument and then often occurs about the peno-scrotal angle or in the bulb. In the "bladder stone age" the commonest cause was a lithotrite. Of recent years, the resectoscope, the cold punch and especially a badly obturated operating cystoscope, have become much more common offenders. Very occasionally, a foreign body introduced by the patient can cause an injury. Fig. 1 shows an open safety pin lying mostly in the urethra but the point has penetrated the wall. The patient said it slipped off his apron and as he was a man of 53 years he should have known this. My own view is that it was being employed as a stimulant for orifice eroticism and slipped into the bulbous urethra. In attempting to manipulate it out, the pin must have opened and the pointed end perforated the urethra. Severe stricture involving a large part of the canal has been caused by injecting an irritant along the urethra. This may have been accidental but has occasionally been intentional as in an attempt to produce a disability in order to avoid war service.

Stricture following External Violence

Much more commonly a stricture is due to rupture of the urethra by external violence and such cases can be divided into two main groups: (1) those affecting the bulbous urethra which are extrapelvic (Fig. 2), and (2) those very near the membranous urethra which are usually intrapelvic (Fig. 3). In the first group the rupture of the urethra has followed a blow in the perineum whilst in the second group it is usually associated with a fracture of the bony pelvis. This grouping is not entirely constant, however, and, especially in children, a fracture of the pelvis may produce an injury of the anterior urethra and as the prostate is dislocated the proximal segment of the urethra is pulled up through the triangular ligament (Fig. 4).

Preliminary investigations.—It is most important before deciding on the best line of treatment that certain investigations should be undertaken. If the patient can void urine, the act should always be observed. A bacteriological examination should be made and the sensitivity of any organism found determined. Intravenous pyelography and a urethrogram with both ascending and, if possible, descending pictures should be made. A urethrogram may show that there is more than one stricture in the urethra (Fig. 5). Multiple strictures in the anterior urethra are unsuitable for treatment by excision and if the condition is to be eradicated a major plastic procedure is necessary. Urethroscopy should always be performed if excision of a stricture is contemplated, since direct vision will show whether or not the remaining part of the urethra is normal. If this is not so, the lumen at the line of suture is much more liable to contract with the formation of a further stricture and for this reason, of course, inflammatory strictures cannot often be treated by simple excision.

Treatment.—The treatment of traumatic stricture will depend on the severity of the symptoms and the position of the lesion. If the stricture only requires dilatation two or three times a year and gives rise to little in the way of symptoms, if the stream is quite good, and this should always be observed, this regime of intermittent dilatations should be continued. If, on the other hand, symptoms or complications are severe, more radical surgical treatment is indicated. In my own series, 18 cases had complications (Table I).

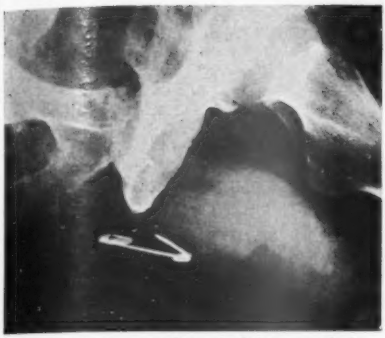


FIG. 1.—An open safety pin lying mostly in the urethra.

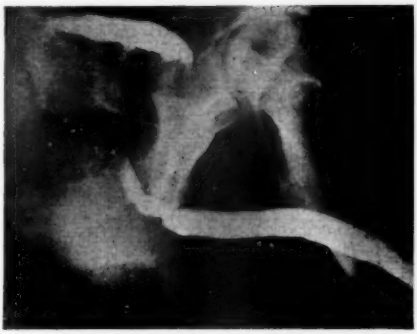


FIG. 2.—Narrow stricture in bulbous urethra.

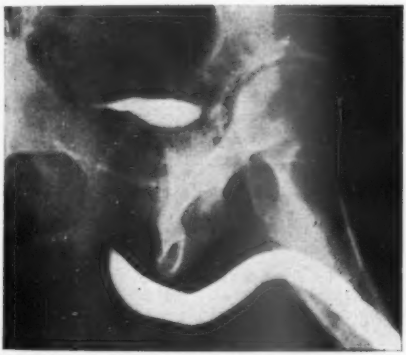


FIG. 3.—Stricture at the triangular ligament.

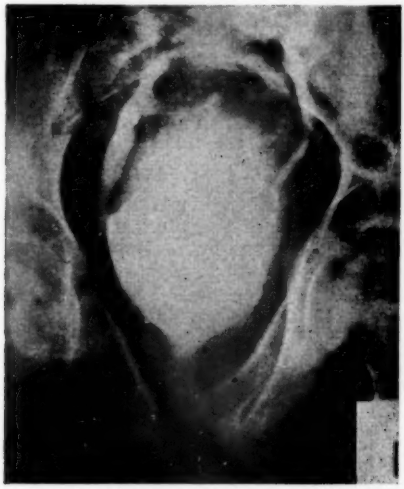


FIG. 4.—Urogram showing some dilatation of the ureters and membranous urethra pulled up after fractured pelvis.

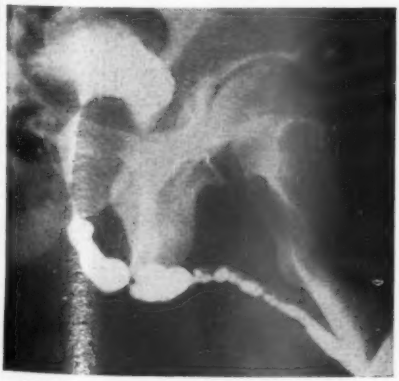


FIG. 5.—Multiple strictures of the urethra.

FIG. 6.—Impassable, impermeable stricture near triangular ligament.

TABLE I.—COMPLICATIONS IN 18 CASES

Suprapubic fistula	11
Perineal fistula	4
Vesical calculus	2
Urethral calculus	3
Diverticulum of the urethra	2

TABLE II.—TYPE OF OPERATION

Urethral pull-through	15
Excision of stricture—Marion	13
Excision of stricture and diverticulectomy	2
External urethrotomy	2

Stricture in the Bulbous Urethra

If, at operation, normal urethra can be identified above and below the stricture, excision of the scar and restoration of the continuity of the canal is possible in the majority. Usually the stricture is either completely cured, or it requires only infrequent instrumentation. In this type of case, I favour the method of Marion.

Marion's operation.—A metal bougie is passed along the urethra as far as the stricture which is then exposed through a mid-line perineal incision and excised. The distal urethra is mobilized, the proximal urethra identified and the two are carefully sutured to each other, using fine plain catgut with the knot tied externally. After closing the roof, a rubber catheter is passed to help in the easy restoration of the continuity of the canal. When this has been effected, the catheter is removed and the bladder is drained suprapubically for fourteen days. Diversion of urine during the healing period is most important and splintage of the urethra is unnecessary. At the end of this time, the urethra is instrumented, and, if all goes well, the suprapubic tube is removed. The patient usually passes water spontaneously, the suprapubic opening closes, and only very occasionally is it necessary to employ an in-dwelling catheter.

Stricture at the Triangular Ligament or in the Posterior Urethra

When the injury of the urethra has been associated with a fracture of the pelvis and a stricture develops, it usually forms very close to the triangular ligament and is frequently intrapelvic. The patient complains of difficulty in passing water with a very poor stream and on examination there may be a very narrow stricture which requires frequent dilatation and each instrumentation may be very difficult. In the worst cases, the stricture is impermeable and often impassable and then all urine is voided through a suprapubic fistula. The majority of these cases are children or young adults. The patient is tremendously handicapped and every attempt must be made to enable him to pass urine naturally.

In 1946 a man, aged 25, was sent to St. Peter's Hospital with a suprapubic cystostomy. He was a farm worker and nine months previously had been run over by a caterpillar tractor. He owed his life to the fact that the ground was very soft at the time but nevertheless he was severely injured, sustained a fractured pelvis, and the prostate was sheared off the upper layer of the triangular ligament tearing the urethra across. It had not been possible to pass an instrument along the urethra at any time since the injury. There was an impassable stricture demonstrated instrumentally and by urethrogram (Fig. 6). The retropubic space and perineum were both explored and a block of fibrous tissue was found separating the prostatic from the bulbous part of the urethra. An operation was performed whereby the bulbous urethra was pulled through into the prostatic part of the canal and the continuity thereby restored. Functionally, this was completely successful (Fig. 7).

I first described this operation in 1948 and have since employed it on a number of cases (Badenoch, 1950).

A urethral pull-through operation.—A mid-line incision is made in the perineum to expose the raphe of the bulbous cavernosus muscle. I prefer this incision to the curved horseshoe one as it gives better access especially to the distal urethra. A sound is passed along the urethra from the external meatus until it is felt obstructed by the stricture. The urethra is divided just distal to the stricture and is mobilized for 3–5 cm., the length depending on the size of the patient. If a suprapubic fistula is already present, the track is excised, otherwise the bladder is opened and a sound is passed through the internal meatus along the prostatic urethra. If the fibrous block is dense the tip of this sound cannot at first be felt. Scar tissue is excised until the tip of the sound is reached and the instrument is then forced out into the perineal wound. The opening is dilated up to 24 Charrière size in an adult. A small sound is now passed retrogradely and its tip made to present in the perineal wound. The open end of a rubber catheter is threaded securely over this tip, and the sound carrying the catheter is brought back into the bladder and out on to the abdominal wall. The tip of the catheter is passed retrogradely along the mobilized bulbous urethra and sutured to it with 2 or 3 stitches. Traction on that end of the catheter lying on the abdominal wall now pulls the bulbous urethra into the prostatic. Traction is kept up by clamping a long pair of pressure forceps across the catheter and these lie tightly against the abdominal wall. The outer wall of the urethra is attached to the lower aspect of the triangular ligament or what is left of it with two or three sutures. The opening in the perineum is sutured, and the abdominal wound is closed round a self-retaining tube which drains the bladder.

Post-operative course: The catheter remains in position for six to eight days after which

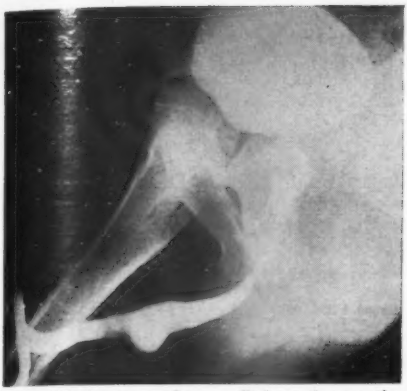


FIG. 7.—Urethrogram after a pull-through operation.

time it is found to have become detached and is therefore removed. Fourteen days after the operation a sound is passed along the urethra and the suprapubic tube removed. The majority of patients pass urine spontaneously and the suprapubic wound heals. In some, an in-dwelling urethral catheter has been necessary for a few days to heal the suprapubic fistula. Sounds are passed at gradually lengthening intervals until the patient can go for a year without instrumentation, after which period he is probably cured.

Results.—During the past eight years, I have performed an open operation on 32 patients with narrow traumatic strictures (Table II). 15 have been dealt with by a pull-through operation. 13 have been treated by excision of the fibrous area and restoration of the continuity of the canal by direct end-to-end suture, 2 in addition had diverticulectomy, 2 have been treated by simply incising the stricture by an external urethrotomy and one of these appeared to be cured of the stricture.

There have been no deaths in this series and no patient has been made worse. 11 patients with suprapubic tubes have been able to discard their contraptions. 4 patients have been cured of perineal fistula. Incidentally, one of these was in an old shepherd from the mountains of North Wales, who had had a perineal lithotomy done in the '80s and had had a fistula for sixty years. Two have had diverticula excised. 5 patients had stones in the bladder or urethra, and 1 had a fragment of bone in the bladder. A considerable number appear to have been completely cured of their difficulty in micturition and no longer require treatment. Almost all the remainder have a better flow and require less frequent instrumentation than previously. One boy has a urethro-rectal fistula which inconveniences him far less than the suprapubic tube with which he was admitted. One patient has considerable incontinence and one occasionally wets the bed at night. I failed at the first attempt with the pull-through operation in 3 patients. In at least one of them I think I did the wrong operation as I had not observed that the membranous urethra had been pulled up through the triangular ligament. I re-operated on 2 of them and they are now passing water, whilst the third was dealt with by Mr. D. I. Williams.

A young man disappeared for three years and was thought to be all right. He had been involved in a pile-driving accident on the Thames, and had sustained a very severe injury. He came under my care eight months after the injury. The first stage of the treatment consisted of lifting off half the right pubic bone which had sequestrated and was lying loose in a suppurating wound. Later a pull-through operation allowed him to pass water normally and the suprapubic fistula closed. He attended out-patients for about two years and then disappeared. After an interval of three years, he turned up complaining of further difficulty and a small suprapubic fistula. Grating was felt on passing a metal sound and on X-ray a large stone was seen to have formed in the bladder and several bits of gravel were seen in the urethra. All these were removed and a 24 Charrière instrument passed easily into the bladder. He is again dry and passing water satisfactorily.

Finally, a few words about the sexual function. In traumatic cases, since the question of compensation is often paramount, this is always a most important factor in the case. It is my experience that a high proportion of injuries of the urethra in adults is followed by impotence. I have heard it said that in every case the power of erection is diminished or absent. This is not so in my series, although I have found that nearly 40% of adults with an intrapelvic injury are impotent. Of those I have been able to question, 2 became normal after a pull-through operation, 3 remained impotent, 2 were potent before and after operation, and 1 became impotent. It is not yet possible to ascertain the effect in the considerable number of children in this series.

The pull-through operation has been done with success by some of my colleagues at St. Peter's Hospital, and several series of successful cases have been published by Villanueva (1953), Rau (1953) and others. I believe that this operation offers a better alternative than uretero-colic anastomosis in the case of an impassable impermeable stricture near the triangular ligament when the continuity of the canal cannot otherwise be restored.

Summary.—In order that the most appropriate treatment for traumatic stricture can be given, we should see the patient pass water. The urethra, when possible, should be inspected along a urethroscope, failing which its calibre should be tested with graduated bougies.

X-rays are most important. Intravenous urography, a micturating urethrogram when the stricture is permeable and a retrograde urethrogram should always be done, and lastly the stricture explored at open operation before deciding on the exact steps of the operation.

REFERENCES

BADENOCH, A. W. (1950) *Brit. J. Urol.*, **22**, 404.
RAU, V. M. (1953) *Indian J. Surg.*, **15**, 255.
VILLANUEVA, A. (1953) *Rev. Urol. Caracas*, **11**, 49.

Professor J. Chassar Moir said that some of the bad results attributed to the presence of an in-dwelling catheter might be caused by the toxic substances which seem to be present in all forms of rubber. In his work as a gynæcologist he frequently had to leave a catheter in position for many days, and he now used polythene or plastic tubing exclusively. This caused far less irritation and was perfectly adequate for drainage purposes. He wondered whether the results described in male surgery might be improved, and the use of an in-dwelling catheter looked upon with less disfavour, if a polythene tube was substituted for the traditional rubber catheter.

Mr. E. W. Riches said that there seemed to be general agreement that rupture of the urethra was followed by stricture and it seemed to him that the more modern treatment of stricture described by Johanson (1953) and by Swinney (1952) should be applied before the stricture was formed. He had waited for an acute rupture of the urethra in order to put it to the test.

The patient was a man of 44 who fell off a ladder. He had the usual signs of extrapelvic rupture with blood coming from the meatus, extravasation into the perineum and scrotum, and retention of urine, and no catheter or bougie could be passed. A small suprapubic catheter was put in and the perineum was explored. The urethra was completely pulped and no repair was possible. The wound was left open with what was left of the urethra stitched to the edges of the skin. At the end of the six weeks the edges were healed and the strip of regenerated mucous membrane was buried by the usual technique. The wound healed save for a small pin-point fistula which had to be excised later. A cavity developed at the site of the repair rather than a stricture. This made instrumentation difficult but the man passed a good stream and had not been dilated for six months. Urethroscopy showed a few hairs at the site of repair which might give rise to trouble later on.

With regard to intrapelvic rupture in fracture of the pelvis a common orthopædic method of management appeared to be suspension of the pelvis in a sling. He described one patient in whom this procedure had produced so much overlapping of the two halves of the pubic symphysis that there was complete obstruction of the urethra by bone and no instrument could be passed. He did not think a pull-through operation would have been possible and he had to do a uretero-colostomy to avoid leaving a permanent suprapubic fistula. The man was well five years later and had married, but he felt that transplantation of the ureters ought not to be necessary for rupture of the urethra.

He agreed entirely with Professor Chassar Moir on the use of the rubber catheter. The red rubber catheter contained sulphur and caused urethritis. Latex catheters were less harmful but plastic catheters were best in cases where an in-dwelling catheter was necessary.

REFERENCES

JOHANSON, B. (1953) In: Modern Trends in Urology. Editor E. W. Riches. London; p. 344.
SWINNEY, J. (1952) *Brit. J. Urol.*, **24**, 229.

Mr. John Swinney said that he thought sufficient experience had been accumulated to say with confidence that by using a strip of buried epithelium it was possible to make a new and useful urethral tube. Whether the epithelium was mucosa from the original urethra, whether it was skin, or a combination of both, really did not matter. He was very interested to hear Mr. Riches describe his case, and he thought it justifiable to examine this new principle and adapt it to the treatment of trauma of the urethra generally.

In a case of rupture of the urethra where the ends could be identified and approximated, he thought it would be reasonable, having done suprapubic cystostomy and drained the perineum, to fashion a wide strip of epithelium and bury it, and leave it, and he was quite sure that a new urethral tube would grow and there would be no stricture formation.

In cases where the urethra was completely destroyed over an area he thought they could justify, as Mr. Poole-Wilson had shown, bringing both the proximal and distal cut ends of the urethra to the surface and suturing the ends of the urethra to the skin. A strip could later be formed, including the cut ends, and buried so that the new urethra would grow.

Mr. Swinney then showed a diagram outlining the buried strip which formed the new tube. The anterior urethra could be reconstructed right from the bulb to the meatus, or any part of it, so that it was possible to get a complete new urethra using this idea. (Mr. Swinney showed further diagrams illustrating the progress of the operation.)

A criticism of the technique was the difficulty in creating a satisfactory external meatus,

and rather than bury a skin tube in the glans penis it was wise to finish the new urethra as a glandular hypospadias. The posterior end where the bulbous urethra joined the membranous urethra was sometimes a difficult area to get healed and properly epithelialized, and the best way was to splint the urethra with a polythene tube into the bladder, and the urethral epithelium and skin would grow and an epithelialized perineal fistula would form, and once that happened one could start making a new urethra. He thought polythene was much better than rubber for that purpose.

Mr. F. R. Kilpatrick in discussing intrapelvic rupture of the urethra stressed the importance of exerting traction on the in-dwelling catheter to keep the ends of the urethra in apposition. The catheters he used were either a De Pezzer catheter or Foley catheter. A Foley catheter with the tip cut off could be threaded over a metal bougie passed down from the bladder in a retrograde manner. He found Hey Groves bougies most useful for this manœuvre as the curve of this bougie allowed it to be passed easily from the bladder down the urethra and out of the external meatus.

He showed an intravenous cystogram of a case where traction had not been applied; here the bladder was lying very high in the pelvis. In cases where there was considerable dislocation of the pelvis with separation of the symphysis pubis he advised open operation to wire the pubic bones together.

Mr. J. Gabe said he had recently had 6 cases of ruptured urethra; 4 were intrapelvic ruptures. One case of intrapelvic rupture had been dealt with by a traumatic surgeon: the bladder was closed by immediate suture. Nevertheless the post-operative course was uncomplicated and normal micturition was resumed after three weeks.

Who was primarily responsible for these patients: the general surgeon, the traumatic surgeon or the urologist?

Securing of the in-dwelling catheter was very important. In one case, the inflated bag of the Foley catheter had become pulled into the urethra, causing still wider separation of the divided ends of the urethra. The result was bad.

Attempts to pass urethral catheters should only be made in the theatre, so that if unsuccessful, further procedures could immediately be carried out.

Professor Chassar Moir showed colour slides demonstrating urethral injuries in the female. Some were the result of obstetric injuries and some of gynæcological operations such as colporrhaphy. He believed that the reason for many of these operative injuries was the formation of a hæmatoma which later became infected. Some of the slides illustrated partial urethral destruction; others showed sloughing of the urethra in its whole length.

The essential of repair was the reconstruction of the urethral "gutter" round a polythene tube which acted as a splint and, later, as a means of drainage. It was extremely important to go above the neck of the bladder in order to infold and strengthen the muscle wall of the vesico-urethral junction. The main union was by a series of nylon sutures inserted mattress fashion to bring about a broad approximation of the freed vaginal wall. Relaxation incisions made well out from the side of the repair were sometimes necessary to relieve tension. The bladder was drained for fourteen days and the nylon stitches were removed on the twenty-first day.

Mr. F. J. Milward said that those who worked in coal-mining areas saw a fair share of these injuries and they were apt to occur in people who could not stand a great deal of surgery. Mr. Cyril Nitch, when he was his registrar, showed him a 16/20 sound with a hole drilled through the tip which could be passed down the penis or from the bladder and a catheter attached to it by a thread passed through the hole in the tip. It was quicker and more certain than threading the end of a catheter on to a sound.

Mr. A. Roche asked why no catheter was to be used in an extrapelvic urethral rupture, whereas an in-dwelling catheter was allowed following repair of an intrapelvic urethral rupture.

Mr. Poole-Wilson in reply, said that when the urethral repair was carried out by the suprapubic route it was never possible to achieve an adequate suture of the divided ends of the urethra. Even if a satisfactory suture were obtained the danger of a further breakdown occurring was great as the pelvic girdle had usually been fractured and its instability allowed considerable movement of the pelvic floor and soft tissues. A urethral splint therefore was a necessity.

Mr. Riches had described a most interesting repair of the bulbous urethra. This means of repair was originally used by Guyon and Legueu in 1902 and was later popularized in France by Pasteau and Iselin in 1906 and 1931. When the damage to the bulbous urethra was great there would seem to be a very definite place for this operation.

As to the treatment of the fractured pelvis, irregularity of the pelvic floor resulting from unreduced fractures or dislocations could give rise to considerable distortion of the prostatic

and membranous urethra. The reduction and stabilization of the fractures and dislocations were difficult problems.

Mr. Badenoch in reply, said he would have tried a pull-through in the case which Mr. Riches showed of the very divided pelvis. He had had 2 patients whose fractures were about as bad as in the case shown. One had done fairly well. The other had had a stone in the urethra since the pull-through operation and had this removed. He still had a stricture but he seemed to keep going on intermittent dilatation. There was an odd grating when a sound was passed and he was not sure whether this was due to grit or to the pelvis, but the patient continued to pass water without much trouble to himself.

[*February* 23, 1956]

"Essential" Hæmaturia

By E. W. RICHES, M.C., M.S., F.R.C.S., and A. C. THACKRAY, M.A., M.D., B.Chir.
Middlesex Hospital, London

IN the first edition of Osler's Medicine (1892) is the following passage: "And, lastly, there are cases in which hæmaturia occurs for a long time without discoverable cause, particularly in young persons. The health may not be seriously impaired. Gull has characterized, in a happy way, a case of this kind as one of renal epistaxis."

The term "essential" hæmaturia, whilst possibly preferable to "renal epistaxis", is used in the sense of idiopathic or independent of other disease (Webster, 1932) and is still a misnomer or a confession of ignorance. What is essential is investigation, and we have selected a few recent cases to illustrate the scope of the investigations needed and the difficulties of diagnosis.

In 1933 Debenham studied 742 cases of hæmaturia at the London Hospital and found that 9% of them were unexplained. Twenty years later a study of 1,000 cases at the Middlesex Hospital (Riches, 1953) showed that only 1·8% were unexplained; this fivefold reduction was due to the advances made in diagnostic methods, and particularly to the introduction of excretion urography which was not available for the investigation of the cases recorded in 1933. Nevertheless cystoscopy during bleeding is still the most conclusive procedure; it must be done with an irrigating cystoscope with the exercise of adequate time and patience. Most of the bladder causes of bleeding will be recognized readily on cystoscopy and the detection of renal hæmaturia, which is our present concern, depends on seeing a bloody efflux from the ureter rather than on passing a ureteric catheter with its attendant slight trauma. All the usual radiological investigations must be done; even though they are generally negative they must often be repeated after a suitable interval if the cause of bleeding has not been discovered. We must admit, too, that the true diagnosis is frequently only made after nephrectomy, and not always then. Dukes (1948) reported the findings after nephrectomy in 9 cases with normal investigations; he found that in four there were hæmorrhages in the pelvic mucosa, designated as renal purpura following the description of Kidd (1928); in 3 there was an angioma of a pyramid, which he regards as an area of vascular granulation tissue rather than a neoplasm or a vascular malformation; in one, which I shall mention later, there was a microscopic adenoma in the kidney, and in one a small tuberculous ulcer.

A man of 73 had intermittent painless hæmaturia for four months. His prostate was slightly enlarged and he had mild prostatic symptoms not demanding operation. Cystoscopy, not during bleeding, showed a normal bladder with a small vascular area on each side of the prostatic margin; the efflux from each ureter was clear. Excretion urography showed normal kidneys and a small prostatic filling defect. He was allowed home. A year later hæmaturia recurred and he was readmitted. This time it was possible to cystoscope him during bleeding and after he had developed pain in the left loin. The efflux from the left kidney was bloody, and a pyelogram showed a distorted pelvis with evidence of contained clot. An immediate nephrectomy was done, and a bulky kidney removed. It contained a papillary transitional cell carcinoma of the upper calyx with no deep invasion.

Retrograde pyelogram a year earlier would probably have shown a filling defect, and the evidence of excretion pictures is not always reliable. The decision to explore was made easy by the eventual discovery that the blood came from the left side. This was an example of the "prostatic decoy", so aptly named by Mr. Adams (1950).

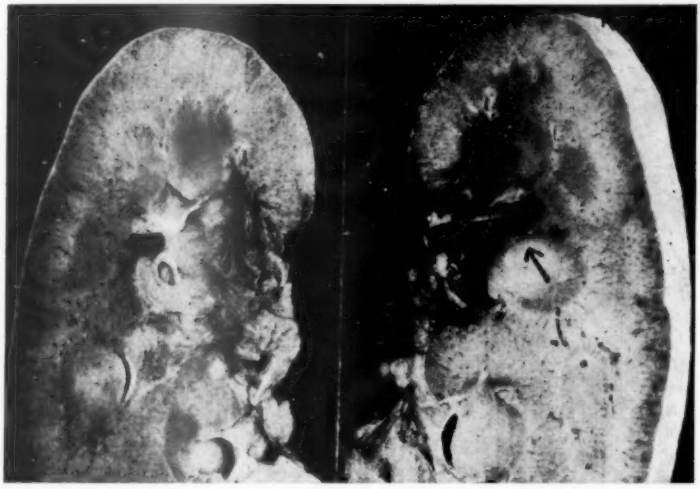
When bleeding has stopped before cystoscopy and the side affected is not known the decision is more difficult. Slight pain in one or other loin may be a pointer, but in itself is not conclusive. In such cases all the resources of radiology, including aortography, will be needed.

A man of 55 had two short episodes of hæmaturia, with a little pain in the right loin. Excretion urography was equivocal although the right side was not so well filled as the left. Cystoscopy revealed no abnormality, and a right retrograde pyelogram was no more than suspicious of a lesion.

The aortogram showed what appeared to be a small area of pooling in the middle of the right kidney, and on the combined evidence of these findings the right kidney was explored. It appeared normal and it was hard to be certain whether there was some induration in it or not. The kidney was removed, and on section it showed a small adenocarcinoma at the site of the pooling.

Exploration in these cases almost always means excision, and it was the confirmation provided by the aortogram that led to the early removal of a new growth in this patient. When the side of bleeding is known with certainty there is more justification for the removal of an apparently normal kidney, especially if the patient is past middle life.

A man of 44 had painless hæmaturia two weeks before he was seen. Cystoscopy showed cystitis and excretion urography was normal; he was treated medically for the cystitis. Bleeding did not recur for over two years when he reported as instructed and was promptly cystoscoped. He was bleeding from the left side, the urine was now sterile, and both excretion and left retrograde pyelography were normal. This was in 1947 before we were using aortography, and in view of his age, now 46, the left kidney was explored and an apparently normal kidney removed. It was sent uncut to Dr. Dukes who found a small area of hæmorrhage in the peri-pelvic fat near the upper calyx (Fig. 1A). It was derived from a small branch of one of the renal vessels around which there was



A B

FIG. 1.—A, Hæmorrhage in the peri-pelvic fat near the upper calyx. B, Deeper dissection showing blood tracking around a branch of the renal artery.

bleeding (Fig 1B), and was traced to a minute adenoma (Fig. 2). This careful dissection gave the answer to one of the causes of "essential" hæmaturia.

The 3 patients mentioned were in the eighth, sixth, and fifth decades respectively; in those of a younger age group the presence of a malignant new growth is less likely and removal of the kidney is undertaken less lightly.

A woman of 25 first bled when she was 16. Cystoscopy, excretion urography and urine examination were all normal, and as no bleeding was seen at the time of cystoscopy she was sent away. Six months later hæmaturia recurred; she was cystoscoped and found to be bleeding from the left kidney. Left retrograde pyelography was normal and there was no evidence of tuberculosis. As her hæmoglobin was 97% and bleeding had ceased she was again sent out. Eight months later she again bled from the left kidney. An aortogram was done and showed no abnormality. The hæmoglobin had fallen to 86% and nephrectomy was performed. The kidney contained a hæmangioma of one calyx and the adjacent pelvis.

This condition, although uncommon, is probably the most frequent cause of "essential" hæmaturia in a young patient. In 1935 Jocelyn Swan and Balme collected 27 cases from the literature; by 1951 Weyrauch and Berger had found 76 cases including one of their own in which the condition was bilateral. The possibility of both kidneys being affected is an argument for conservatism in surgery.

We have one patient who probably has an angioma who has not yet undergone operation.

This woman of 25 first bled when she was 21 and was investigated elsewhere with negative results. Our repeated investigations have shown bleeding from the right kidney, normal excretion and retrograde pyelograms except for a little dilatation of the right upper calyx, and a normal aortogram

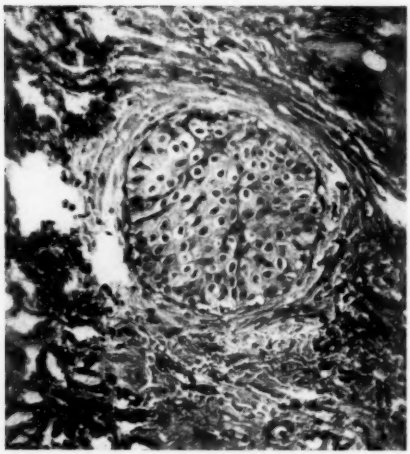


FIG. 2.—Small adenoma found near the point marked with an arrow in Fig. 1B. (Figs. 1 and 2 by courtesy of Dr. Cuthbert Dukes.)

with a suggestion of fœtal lobulation in the nephrogram. She is now, after five years, getting an occasional ache in the right side and will probably come to operation. Her hæmoglobin is 87%.

INDICATIONS FOR EXPLORATION

When the side of bleeding is known we consider that exploration should be done in the following circumstances:

(1) On the slightest suspicion of new growth.
(2) If hæmorrhage is frequently repeated.
(3) If constitutional effects of blood loss become apparent.
(4) If pain is persistent on the affected side.
(5) If the patient is over 40.

The diagnosis of renal or vesical purpura is difficult to maintain in the absence of other purpuric manifestations, but hæmatology is advancing and it has recently been possible to revise this tentative diagnosis in one patient with the aid of a somewhat complicated test carried out by Dr. J. W. Stewart.

A woman of 34 first had hæmaturia at the age of 27. She had been extensively investigated elsewhere with negative results. Cystoscopy showed multiple hæmorrhagic spots on the bladder base which bled on distension or on emptying but no blood was ever seen from either ureter. The urine was free from pus and sterile on culture and the bladder capacity was normal. Pyelograms, aortogram and perirenal oxygen insufflation showed normal kidneys. Hæmoglobin was 95%, and the blood count, platelets, coagulation time, clot retraction and bleeding time were normal. At this stage Dr. Stewart carried out a thrombin generation test (Table I). It showed that she generates

TABLE I

THROMBIN GENERATION TEST

Time in minutes	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Control	*none*	*220*	*42*	*44*	*25*	*22*	*21*	*24*	*35*	*52 seconds*
Patient	———		*none*	———	*165*	*80*	*60*	*40*	*42*	*55 seconds*

thrombin poorly and late, no demonstrable quantity being present until five minutes as against the control's two minutes. The thromboplastin generation test gave similar results. It appears that she has a coagulation defect of the type described by Rosenthal *et al.* (1953) and labelled plasma thromboplastin antecedent (P.T.A.) deficiency. The condition is inherited apparently by a simple Mendelian dominant, and may be allied to hæmophilia and Christmas disease. There is no known permanent cure, but transfusion of stored blood is an effective corrective. Bleeding is said to be most likely to occur after operations or trauma. Her brother also has hæmaturia, but has not yet been tested.

She had also been looked on as a case of low-grade nephritis despite the absence of casts. Thomson-Walker (1923), investigating patients with renal hæmaturia of obscure origin, found cortical patches of fibrosis in 13 cases submitted to renal biopsy, and such localized nephritis has been considered a cause of unilateral renal hæmaturia, but the evidence for it is not convincing.

Finally we must mention 2 patients who are really the *raison d'être* of this paper.

A man of 64, who first had hæmaturia at the age of 57, came up in 1949. He had some prostatic enlargement but few symptoms, and cystoscopy and excretion urography were normal. He bled intermittently but it was not until nearly five years later that we were able to cystoscope him during bleeding and find that the blood came from the right kidney. A right pyelogram showed slight dilatation of the upper calyx (Fig. 3). An aortogram was normal (Fig. 4). By this time his prostate was larger and was causing obstruction and it was removed in 1954. He remained well for ten months when hæmaturia recurred, but less severely. However it continued and was found again to come from the right kidney. His hæmoglobin was 82%, and no coagulation defect was demonstrable. He was readmitted in due course and the hæmoglobin had fallen to 51%. After transfusion of three pints of blood had raised it to 74% his right kidney was removed.

The kidney, which was removed, appeared quite normal externally, but when bisected some blood was seen in the upper calyx and there was an ill-defined dark red vascular area at the apex of the corresponding papilla (Fig. 5). Microscopically there were numerous thin-walled cavernous blood

FIG. 3.—Retrograde pyelogram. There is a little dilatation of the upper calyx but the pyelogram is essentially normal.

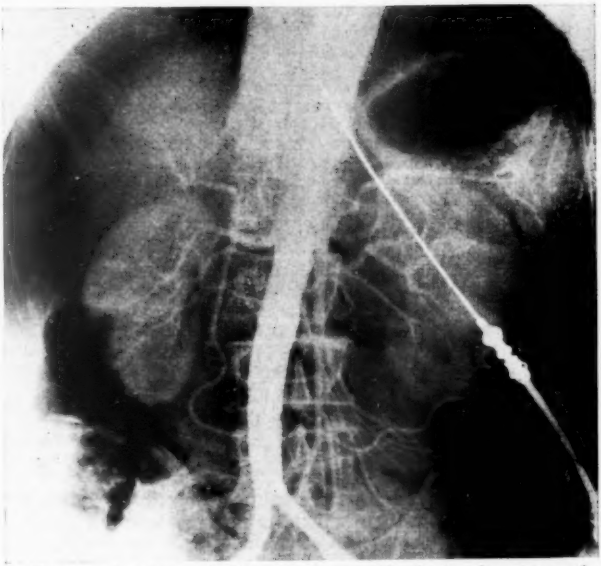
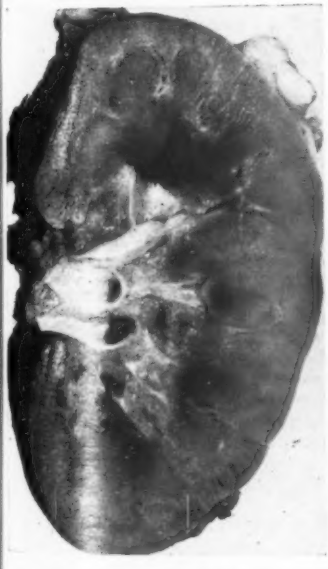


FIG. 4.—Aortogram in the same case as Fig. 3, showing a normal vascular pattern in both kidneys.



← FIG. 5.—The excised kidney from the same case. The upper and lower calyces each show a vascular area at the apex of the papilla. (Right kidney seen from behind.)

FIG. 6.—Section from the upper calyx of Fig. 5. There are large cavernous blood spaces among the tubules opening on to the renal papilla. Site of rupture and source of hæmorrhage indicated by X. (× 69.)

spaces at the apex of the pyramid among the terminal collecting tubules, and serial sections showed fibrinous clot at the site of rupture of one of these dilated vessels (Fig. 6). The appearances suggested a varicosity of the existing small vessels of the part due to local venous congestion, rather than a true angioma. This view was strengthened by the discovery of a minor degree of similar vascular dilatation of the papilla of the lower calyx. The kidney substance showed no abnormality apart from some altered blood pigment in the tubular epithelial cells, probably related to previous transfusions.

The other patient was a woman of 57 with left renal pain and hæmaturia. She had been completely investigated two years earlier by Mr. N. L. Shepperd to whom I am indebted for his notes and a pyelogram. His conclusion was that the kidney was too good to warrant exploration. Her bleeding started after eating fruit, especially gooseberries. She said that even one fruit sweet or a strawberry ice cream brought it on, but despite every provocation it was two years before we were able to see her during an attack and find blood coming from the left ureter. In the interval repeated excretion pyelography had shown normal kidneys and an aortogram had been normal with no visible extravasation of blood from the aorta when this was done. She never bled whilst in hospital until January 1956 when we managed to start it by giving her a meal of plums. Although she was considered a case of oxaluria oxalate crystals were never found in the urine despite repeated search.

An excretion pyelogram during bleeding showed the patchy filling defects of clot in the left renal pelvis and a left nephro-ureterectomy was carried out. At operation there were considerable perinephric adhesions and some hæmatoma formation which may possibly have been a relic of the aortography nearly three years previously; the kidney was enlarged and the upper 3 in. of the ureter thickened in the manner of a papillary tumour of the pelvis.

When the kidney was split open the pelvis was found to be narrowed and full of granular blood clot, and the apparent enlargement of the pelvis and upper ureter was seen to be due to extensive hæmorrhage into the peripelvic fatty tissue, much of which was necrotic. Microscopical sections of the peripelvic tissues confirmed the presence of considerable areas of fat necrosis and old interstitial hæmorrhage, the appearances being compatible with the extravasation of blood at the time of the aortography. After many sections had been examined without finding a cause for the original bleeding, a small area of papillomatosis of the upper part of the pelvis was discovered, which had been masked by the blood clot in the pelvis, and the appearance of which was atypical due to hæmorrhage into the cores of the papillary processes.

Conclusions

It should be our aim to eliminate the term "essential" hæmaturia from the medical dictionary. Careful and complete investigations are necessary if this is to be done. Excretion urography has lessened the number of retrograde pyelograms, but the latter examination should not be omitted in cases of this kind. Aortography may pick out an early parenchymal tumour of the kidney, but cystoscopy during bleeding remains the sheet anchor of diagnosis. If bleeding has stopped the patient should be instructed to return at once when it starts again, for immediate cystoscopy. Renal angiomata are probably more common than has been supposed, and more advanced hæmatological investigations may elucidate some cases of unexplained hæmaturia.

REFERENCES

Adams, A. W. (1950) *Brit. J. Surg.*, **38**, 210.
Debenham, R. K. (1933) *Brit. J. Surg.*, **21**, 44.
Dukes, C. E. (1948) *Trans. med. Soc. Lond.*, **65**, 393.
Kidd, F. (1928) *Proc. R. Soc. Med.*, **21**, 1105.
Osler, W. (1892) Text Book of Medicine, New York and London: p. 723.
Riches, E. W. (1953–54) *Trans. med. Soc. Lond.*, **75**, 1.
Rosenthal, R. L., Dreskin, O. H., and Rosenthal, N. (1953) *Proc. Soc. exp. Biol., N.Y.*, **82**, 171.
Swan, R. H. J., and Balme, H. (1935) *Brit. J. Surg.*, **23**, 282.
Thomson-Walker, J. (1923) In: Choyce's System of Surgery, 2nd edition. London: **2**, 815.
Webster, N. (1932) New International Dictionary. London.
Weyrauch, H. M., and Berger, M. M. (1951) *Stanf. med. Bull.*, **9**, 43.

The President said that the problem of hæmaturia from one kidney was an ever-recurring one and in the absence of pyelographic defects and, as had been seen from Mr. Riches' pictures, aortographic defect, what was one to do?

Mr. Riches had mentioned the possibility of a blood dyscrasia where bleeding might occur from the contralateral kidney or from the bowel; he also was acquainted with that problem. Urologists had to make use of every ancillary science in tracing hæmaturia; the pathologists had shown what careful section could do to trace the source of essential hæmaturia; a faulty pyelogram or a doubtful defect was rarely due to error in technique but due to essential pathology. He doubted very much whether a thoughtful urologist had ever removed a kidney without good reason.

Mr. Wilfrid Adams mentioned 3 cases, one of which linked on to the President's last statement about hæmaturia due to constitutional causes.

The first case was a man of 25 whom the physician tried very hard to persuade him to cystoscope, but he happened to know that the patient was a hæmophiliac and he preferred to see him bleeding rather than to operate on him. Later, he resumed work.

The next patient was a robust man about 30. He was bleeding heavily and on looking at the bladder blood was seen issuing from both his kidneys. What was the cause? Radiography was impeccable apart from some hyperplasia; he was a big man and had big kidneys. That was in 1946. His bleeding recurred in 1948 but he would not accept cystoscopy. He

thought one could call it an idiopathic bilateral bleeding, and he would emphasize that for the younger people who doubted it.

The next case was a woman of 45 who was sent up to him two years ago with hæmaturia. She had been bleeding for five years. She was a very bad colour and he thought his general practitioner colleague had been a little negligent. He then found, and at well-spaced occasions since, including early 1956, issuing from the right kidney, a moderate stream of blood. Everything was negative apart from the bleeding. He asked that she should come up when she was bleeding as no bleeding occurred when she was in hospital. This brought him to Mr. Riches' first quotation, characterizing essential hæmaturia as a long-lasting trouble, and that was the point.

What would make one suspect the case as possibly idiopathic? Was it commoner in women and young people? It was likely not to be heavy; whereas a sudden bout in older people was the thing which agitated him. The importance of genuine essential hæmaturia was inversely proportional to its incidence in that large group, symptomless hæmaturia. It was because essential hæmaturia was a member of that group, in which so much was serious or very serious when investigated, that it signified as an entity. It was easy, having done what Mr. Riches could do in the way of investigation, to say that it was unimportant, he need not worry about it, it was a case of renal essential hæmaturia. It was only when one had examined a patient a few times that one had proved two things: (1) that there was "nothing the matter", and (2) although it was from only one kidney, the surgeon might still be interested because a patient could still exsanguinate and die from a single bleeding kidney. Sufficiently protracted, essential hæmaturia might justify operation.

One must face this matter of symptomless hæmaturia with an open mind and every precaution, expecting trouble rather than readily accepting the alternative diagnosis of essential hæmaturia. One question about Mr. Riches' case: Would one rather be without a kidney with a small angioma in it, or keep the kidney with the small angioma in it, remembering that the other one might one day have the same?

Mr. R. A. Mogg asked Dr. Thackray if any of the sections taken of the cases which he showed were serial sections.

He realized that this was a laborious and tedious task but Dr. McMahon of Boston had described how he had sectioned three kidneys which had bled very mysteriously and he had shown that in certain of the sections there was a direct communication between the endothelium of the peri-forniceal venous sinuses and the transitional epithelium of the calyces. Dr. McMahon also stressed the fact that sufficient attention was not given to the peri-forniceal venous plexuses which occurred round each minor and major calyx, as a potential factor in the origin of essential hæmaturia. He postulated that variations in the intrapelvic pressures would open up these communications between the calyx and the venous sinus and be responsible for bleeding from that area and so produce hæmaturia. The writer quoted 4 cases and showed convincing sections demonstrating the communication between the venous sinuses round the calyces and the epithelial lining of the calyces.

Mr. Mogg wondered if some of these cases of essential hæmaturia actually had this associated lesion. It seemed a logical explanation and one which would account for the mysterious bleeding which occurs from time to time in essential hæmaturia.

Mr. W. S. Mack pointed out that many cases of so-called hæmaturia were not true hæmaturias but were due to other colourings. Where a true essential hæmaturia was present this might be of a short duration or might recur for years. Sufficient attention had not been paid by urologists to vascular changes in the kidney, which undoubtedly did occur during pregnancy where hæmaturia was common. These vascular changes might lead to, as in one case of his own, a sector infarction of a kidney two years after the confinement. This infarction caused very severe bleeding and a pre-operative diagnosis of renal tumour was made. In a few cases where he had carried out a nephrectomy for essential hæmaturia, the pathologist had reported that the kidney was the seat of chronic nephritis.

He very much doubted if angiomata were common though granulomatous changes at the tips of the renal pyramid did occur fairly often and possibly some of them were diagnosed as renal angiomata.

Dr. Thackray, in reply to Mr. Mogg, said that a considerable number of sections had been examined, but they were not continuous serial sections.

He had read the work about the possibility of a communication between the lumen of a calyx and the circular vein in the fornix. To exclude the presence of such a communication would require the examination of serial sections through the whole kidney, almost a life's work. In neither of the cases described was such an extensive examination necessary, as an alternative source of bleeding was found in each.

Mr. G. E. Parker asked why in the first case the diagnosis could not have been one of hæmorrhagic nephritis; there was a fairly positive lesion in the upper pole, but apparently the same type of lesion involved other parts of the kidney. Would hæmorrhagic nephritis explain the degree of keratinization over the surface? Sometimes where there was an excess of blood supply there was hyperkeratinization and he could not see why the first case could not have been a case of nephritic hæmorrhage.

Mr. Hugh Donovan asked what were the chances of a given patient having a tumour after one thorough negative investigation? Having investigated one of these patients with negative results he did not usually investigate him again unless he continued bleeding.

Dr. Thackray, in reply to Mr. Parker, said that the epithelium from the collecting tubule appeared to have extended out over the papilla. The change was confined to the collecting tubules, there was no sign of any nephritis and no indication of inflammation of the kidney. The blood vessels in the other papillæ lower down were markedly dilated but there was no rupture.

Mr. Riches, in reply to Mr. Adams, pointed out that they had tried to show that there was no such thing as "essential" hæmaturia. When there was macroscopic bleeding diligent search ought to discover the cause, whether it was an angioma or even a patch of nephritis as Mr. Parker had mentioned. Bleeding could also occur after excessive exercise or from lack of vitamin C, and one did not remove such kidneys.

In the literature he could find only one bilateral case of angioma of kidney, and one of the great difficulties had been to know when to take the kidney out and when not. He had shown one case where he had waited five years and had not yet taken the kidney out. All the circumstances and all the investigations including aortography must be considered, but he would rather not take a kidney out which contained only a minor lesion. At the same time he would rather not leave a kidney behind which was bleeding especially if the patient had passed middle age. It must be remembered, however, that in almost every case exploration meant excision.

Referring to Mr. Mogg's remarks about the vascular changes in pregnancy, if the patient was not bleeding when she came up one had only her word for it that the urine had been red and that was why cystoscopy during hæmaturia was so important.

In reply to Mr. Hugh Donovan: If these patients were to be investigated completely they must be cystoscoped when they were bleeding if at all possible; it was the most conclusive investigation. It might be interesting to know whether these lesions ultimately showed any change in the X-ray pictures. In one case he had shown, repeated pyelograms had been taken without any change, but if there were any changes they could only be found by looking for them.

Some Observations on Ureteric Activity and Their Clinical Significance

By L. F. Tinckler, F.R.C.S., Ch.M.

Much of the factual information on urinary tract function concerns the kidney and bladder. Interposed between these two important structures, the ureter occupies a less prominent place in the literature, perhaps in keeping with its humble task of water carrier. However, it is an organ which excites interest. Uncommonly affected primarily, it receives most of its pathological insults second-hand from above or below. It is tolerant of surgical assault and can be incised for stone, sectioned and repaired, transplanted on to skin surface or bowel with apparent impunity to its function. What is its function? To convey urine secreted by the kidney to the bladder. Without this service, the complicated structure and physiology of the kidney would be naught. How is this function achieved? This is the question which I shall attempt to answer in the following account of experimental observations on ureteric activity.

Much speculation and controversy has existed on this subject. Broadly speaking, investigators have come to two divergent conclusions. There are those who regard the ureter as autonomous, functioning with an intrinsic mechanism, apart from nervous control and unresponsive to administered drugs. The other view, diametrically opposite, regards the organ as being under nervous influence and its function susceptible to pharmacological alteration.

The position was such that Trattner, leading a discussion on "The Physiology of the Intact Human Ureter" (Lapides, 1948) said, "This investigation should be carefully reviewed by others for either substantiation, modification or change, for then the weight of incontrovertible evidence will surely indicate the proper direction".

It is remarkable that this statement should be made by such an authority nearly a

century after Engelmann's classical paper on the ureter in 1869. Investigating the ureter in humans and animals, Engelmann noted a rich network of nerve fibres in the adventitia. He was uncertain as to the exact role played by the innervation, but concluded that peristalsis was carried out on a myogenic basis and that the smooth muscle was a syncytium, propagating impulses for contraction by molecular activity, an entirely intrinsic mechanism.

In 1922, Harvey Trattner of Cleveland devised an apparatus which he called a hydrophoro-graph, and whereby he recorded via a ureteric catheter pressure changes in the ureter. By this means he found that ureteric activity was affected by a wide range of factors of such diverse natures as pH of the blood and urine, stimulation of the renal pedicle, change of position, bladder pressure and certain drugs. Repeating these experiments, and using a similar technique, Lapides (1948) entirely contradicted Trattner's findings, and opined that the rate of urine production was the only factor influencing ureteric peristalsis, the stimulus of which was distension of the lumen by urine. Any previously observed effect of drugs on the intact ureter was more apparent than real, being solely due to altering renal filtration rate. Thus he dubbed the ureter as a specialized involuntary organ which was probably autonomous.

That a continuous peristaltic wave mechanism is not the whole story of urine propulsion was indicated by Fuchs (1936). In his "Cystoid Theory", he considered the ureter to be composed of a number of functionally separate chambers corresponding to a morphological segmentation. With a sphincter interposed, each of these "little bladders" received urine from the adjacent chamber above and forced its contents on to the one below by a detrusor-like contraction. The cystoids were regarded as booster stations for propulsion and the sphincters present to prevent reflux, cystoids and sphincters allegedly being constant. He considered the cystoids to be under nervous control and operated by opening and closing reflexes activated by afferent impulses from the bladder. This theory has been supported by Begg (1946) who accepted the cystoid mechanism as being the only mode of urine transmission in the human ureter and used it to explain the appearances of the organ as seen on intravenous pyelography.

The position is still highly controversial. More recently, Hanley (1953) has made a notable contribution to an understanding of this subject with his method of ureteric electromyography and it is anticipated that excretion pyelography with image intensified fluoroscopy will produce further valuable information.

The observations which I have the privilege to present resulted from three main phases of investigation carried out by Dr. D. W. Gould, Dr. A. C. L. Hsieh and myself, at the University of Hong Kong (1955). In the first, experimental animals were used. Pressure changes were recorded graphically from the intact ureter and direct observations made of dyed urine passing down the ureters of rabbits. The second phase consisted of a series of experiments conducted on isolated segments of animal ureter. The third was an outcome of conclusions reached from the results of the first two and, in this, bladder pressures were recorded in various postures of human subjects.

The Behaviour of the Intact Ureter in Animals

Pressure tracings were recorded from the ureter of dogs. The abdomen of the anæsthetized animal was opened and the ureter on one side exposed. Hypodermic needles were inserted into the lumen of the upper, middle and lower thirds of the ureter. Polythene tubing connected the needles to strain gauge manometers and simultaneous pressure records made from the three sites by means of an electronic recorder.

Pressures from the top, middle and lower portions are represented on the record in that order from above down. The peaks in the trace are consequent upon peristaltic action and the manner in which the activity of the ureter varies from time to time is shown in respect to base pressure, peristaltic wave amplitude and frequency.

Despite this variability, study of the recordings revealed that the ureter handles the passage of urine along its lumen in two different ways. In one, the urine is propelled along the length of the ureter without pause, to be discharged into the bladder by a peristaltic wave commencing at the top. In the other, urine is conveyed part way only by peristalsis, which then peters out at an intermediate site. The arrival of aggregates of urine from above then increases the size of the so-called "spindle" until it is carried further on its course by the initiation of fresh peristaltic activity. Distinctive patterns are produced in the tracings by these two modes of urine propulsion and have been designated the "through" and "segmental" patterns respectively.

In the "through" method, each peristaltic wave in the upper portion of the ureter is followed successively by pressure waves lower down and a discharge of urine from the ureteric orifice as signalled on the record by a black dash.

The "segmental" mode gives an altogether different picture. Here peristaltic waves from

the top feed urine into the lower portion, giving rise to a progressive increase in base pressure. Further progress of urine is arrested until a level of filling is reached at which peristaltic action is provoked, resulting in an efflux into the bladder.

Repetition of Fuchs' experiments confirmed that the ureter handles the passage of urine in two ways, as was deduced from the pressure tracings. Indigo carmine was injected intravenously into rabbits and the dye-stained urine observed passing along the exposed ureter.

Urine was seen to pass either straight through to the bladder or to become temporarily arrested variously in the top, intermediate or lower portions, separately or in combination.

Such pooling of urine could constantly be produced in the lower ureter by raising bladder pressure. Under such circumstances, the ureter was seen to be continuously distended with urine in the interval between peristaltic waves.

Pooling of urine in the lower segment is explicable on a simple mechanical basis. On raising bladder pressure, the ureter is initially incapable of emptying itself against the increased resistance to ejection. Urine accumulates as a residuum until, by subjecting the ureteral muscle fibres to greater stretch, they are enabled to contract with enhanced vigour and ejection force, in the same way as increased venous filling of the heart results in improved cardiac output.

Segmental activity as manifest by pooling in the upper levels of the ureter can be explained similarly by accepting that ureteric tone is increased when bladder pressure is raised. Greater resistance to the passage of urine will be presented by the tonically constricted lumen impeding progress of urine until pooling occurs to an extent that stimulates more vigorous peristaltic action by stretching the muscle wall.

The fact that anatomical sphincters have never been demonstrated in the ureter lends point to the notion that variations of tone are the basis of segmental function.

That tone exists in the ureter capable of resisting the transmission of back pressure within limits is shown by recording the effect of raising intravesical pressure. Tracings taken from the top and lower portions of the intact viscus reveal that the effect is mainly upon the latter and is reflected either to a lesser extent, or not at all, at the renal end. As this rise of pressure is not communicated to all levels of the ureter, it follows that the intervening lumen must be constricted consequent upon tonic contractions of the muscle wall.

Segmental activity has the attribute of a purposeful mechanism. It exists, most likely, to enable the ureter to work more efficiently against bladder resistance, and is brought about by changes of tone which also protect the nephron from back pressure.

What evidence is there that tone is an entity? and how is it influenced *in vivo*? Peristalsis is an autonomous function and can be observed taking place in a ureter removed from the body. It can be initiated by any mechanical stimulus distending the ureteric lumen as by injecting fluid or by introducing solid objects such as glass beads.

Tone, on the other hand, is not exhibited by the isolated organ. This was demonstrated by carrying out a simultaneous pressure trace from the usual three sites in an excised ureter perfused with saline. Waves of peristalsis were produced identical with those observed in the intact viscus. Pressures, however, throughout the length of the lumen remained equal, the ureter behaving as a simple open tube between peristaltic waves. Addition of acetylcholine to the fluid bathing the ureter was then followed by a difference of pressure being recorded between the top and lower portions and a tracing similar to that obtained from a ureter *in vivo*. That a humoral agent of the autonomic nervous system is capable of restoring tonic activity to a ureter severed of all connexions is significant, in view of the rich innervation which it receives from both parasympathetic and sympathetic divisions.

While such innervation could be solely concerned with sensation it is in keeping with experimental observations that it may also subserve the control of tone.

Pursuing the question of autonomic influence, the effect of acetylcholine and adrenaline on isolated ureters was noted. Segments from the upper, middle and lower thirds were mounted in a tissue bath. A kymographic record was made of their response and the drugs added as required.

Additions of acetylcholine and adrenaline to the bath gave rise to tonic contraction. Atropine and piperoxan, the antagonists of the stimulating agents, produced a corresponding decrement of tone. The response was greatest in the lower segment and progressively less in the middle and upper portions indicating the presence of a tone gradient in the ureter.

The foregone evidence lends support to the notion that the ureter is functionally, as well as anatomically, designed to fulfil its role in the dynamics of the urinary tract and that tone, as distinct from peristalsis, is under the control of the autonomic nervous system.

It is pertinent to enquire why such an elaborate tone mechanism exists at all, as peristalsis alone is apparently adequate to the task of urine propulsion. Resting bladder pressures are commonly supposed to be low, gauged by cystometry as usually carried out. With the subject lying down, values in the region of 10 cm. of water are initially recorded, and increase but

little with progressive filling until detrusor activity occurs preparatory to voiding. If tone is required to protect the kidney, whilst enabling the ureter to work against high vesical pressures, then it would seem to exist solely for the relatively short period of micturition.

However, a more active participation for the tone mechanism can be invoked by observing that, in contrast to the low resting bladder pressure of recumbency appreciably higher values are recorded with the subject standing. Thus it is against pressures of this higher order that the ureter has to feed urine into the bladder for the greater part of twenty-four hours.

If such an increment in bladder pressure on standing was due merely to a general increase in intra-abdominal pressure, the ureter would be affected to the same extent as the bladder. No pressure gradient would be established between the two and the working conditions remain unaltered.

This possibility was investigated by simultaneously recording intra-abdominal and bladder pressure from human subjects in various postures. Bladder pressures were recorded via a urethral catheter and intra-abdominal tension from a balloon swallowed into the stomach. A tilting cradle was used to tip the subject passively into the upright and head down positions.

Tilting feet down into the standing position produced a rise in bladder pressure, accompanied by a fall in intragastric pressure, whilst the reverse was true when the head was tilted down.

This differential pressure change indicates that alteration of posture does not affect the bladder as part of a general change of intra-abdominal tension, for otherwise, vesical and intragastric pressures would vary in the same direction. Rise in bladder pressure on standing is, therefore, an actual increase not shared throughout the abdominal cavity and can readily be accounted for by the weight of the bowel descending on to the bladder fundus.

Summary.—The following brief deductions can be made from this investigation: The ureter is autonomous as far as peristalsis is concerned, but dependent on the autonomic nervous system for the control of tone. Tone is maximal in the pre-vesical portion of the ureter existing to protect the kidney and to enable the ureter to eject against varied bladder pressure as notably obtains when the subject is ambulant.

Clinical Conditions Affecting the Ureter, Discussed in the Light of Experimental Findings

The Ureter in Hyper- and Hypo-tonus

Hydronephrosis

It is interesting to speculate on the relationship of this concept of ureteric activity to certain conditions popularly believed to be due to functional disorder.

Depending as it does on intricate nervous control, there will be greater opportunity for tone disturbance to occur than in the case of peristalsis. Thus it is conceivable that excess or deficiency of tone might exist to an extent that gives rise to clinically recognizable pathology.

Under normal conditions, tone is present to a degree sufficient to fulfil the role of preventing back pressure on the kidney, but short of the level at which it impedes progress of urine down the ureter. If this balance is shifted in the direction of excess, then the ureter will be unable to accommodate urine at the same rate as it is formed, and relative stasis of urine will take place in the pelvis and calyces which will, in consequence, dilate. This dilatation, by submitting the pelvic musculature to greater stretch, will empower it to contract with increased vigour, to force urine into the ureter. A new balance of function will be achieved at the expense of some dilatation of the calyceal system. If no further increase in ureteric tone occurs, then the case will remain as an example of early hydronephrosis of the non-mechanical type and, at this stage, when still wholly functional, normal contour will be restored if ureteric tone reverts to normal.

However, a progressive increase, or a marked initial excess of tone will lead to a degree of dilatation of the pelvis which will become permanent owing to organic changes in the wall. During this evolution of hydronephrosis, there will be no apparent pathology demonstrable in the ureter, the contour of which will be normal, and which will continue to undergo peristalsis, as this activity is unaffected by the functional disturbance.

Among other theories of ætiology of so-called congenital hydronephrosis, obstruction at the pelvi-ureteral junction due to achalasia or spasm is often quoted. However, the existence of a sphincter at that site is not unequivocally proven and it is suggested that non-mechanical hydronephrosis could have its origin in hypertonus of the ureter. The circumstances are comparable to congenital megacolon in which there is a functional derangement of the colon distal to the dilated bowel.

The Chronically Dilated Ureter

Chronic dilatation of the ureter is classified as being either primary—when the causal lesion directly affects the ureter itself, or secondary—when dilatation is the effect of back

pressure arising distally. Amongst the former, idiopathic mega-ureter is unique in having no demonstrable ætiology. Usually unilateral, the conditions may be accompanied by other congenital defects of the urinary tract.

Similar idiopathic dilatation of the urinary tract has been described by Innes Williams (1954) as part of the mega-ureter megacystitis syndrome, by which term he referred to cases exhibiting markedly dilated ureters, disturbance of vesical function with a large capacity bladder and atonic musculature, a wide bladder neck and no obstruction. Quite unrelated to Marion's disease there are some similarities to the state of affairs in the neurogenic bladder, with the essential difference that there is no demonstrable disease of the central nervous system in these patients.

Svenson *et al.* (1952) have suggested that the condition is due to a failure of ganglion cell development in the bladder, and support their view histologically. In the absence of manifest obstruction, the mega-ureter megacystitis syndrome must be regarded as a functional disturbance. Svenson's work has given a clue that the cause lies in the intimate nervous control of bladder function. It is tempting to ascribe the dilatation of the ureter in these cases similarly to lack of tone consequent upon defective innervation. Innes Williams noted that the patients had no residual urine but voided large amounts on micturition at intervals less frequent than normal. This observation is an example of the way in which propulsion of urine by detrusor activity is divorced from muscle tone in the same manner in which the described investigations have shown that tone and peristalsis in the ureter are distinct functional entities.

Another example may be cited of the way in which dilatation of the ureter is associated with a congenital bladder lesion without an element of obstruction. Ureteric dilatation occurs in the condition of ectopia vesicæ. The ureters drain freely on to the malformed abdominal wall, development of the bladder being confined to an imperfect trigonal area. On a mechanical basis, there is no clear reason why dilatation of the ureter should exist, but it is interesting to speculate on the role played by innervation of the ureteric tone in the condition. If afferent nervous impulses influencing tone in the ureter do arise in the bladder wall and excite an automatic reflex arc by variations of vesical distension and pressure, then they will be absent in ectopia vesicæ for either or both of two reasons. Firstly, owing to the absence of receptor nerve endings in the mal-developed bladder and, secondly, because the permanently open rudimentary bladder is never subjected to distension by accumulated urine.

The Transplanted Ureter

For many years it has been technically feasible to divert the urinary stream into the colon by uretero-colic anastomosis for such indications as total cystectomy for carcinoma of the bladder, the systolic tuberculous bladder and ectopia vesicæ. In recent times, dissatisfaction has been expressed about the results of the procedure, the chief bogy of which is ureteral reflux of septic colonic contents with the advent of ascending pyelonephrosis. The importance of a valve mechanism at the lower end of the ureter in preventing reflux has received recognition in some of the operations devised, which provide for an oblique course of the ureter through the wall of the colon simulating the normal uretero-vesical junction. Other procedures by which the ureter is transplanted directly into the colon are liable to stricture formation at the new orifice, unless a mucosa-to-mucosa suture technique is employed, with obstruction to efflux of urine. Whatever method is used, some degree of dilatation of the upper urinary tract appears to be inevitable, and it is pertinent to enquire why this occurs.

There are three factors protecting the integrity of the upper urinary tract under normal conditions.

(1) The flap valve at the uretero-vesical junction.
(2) The ejection power of the ureteral contraction.
(3) The state of tone of the ureteral musculature.

Accepting this, it is clear that any uretero-colic anastomosis that does not provide for a valve removes the first line of defence from a ureter that has to discharge its contents into a viscus capable of developing pressures higher than that with which the other two factors can cope. Further, it can be reasoned that factors 2 and 3 are encroached upon by the method in which the operation is usually performed. Transplantation of the ureter is into the sigmoid colon and, having regard to anatomical disposition and the danger of excessive mobilization of the ureter jeopardizing its blood supply, the latter organ is divided just below the pelvic brim. This excludes the pelvic portion of ureter, which amounts to almost its lower third. It is just this portion of the ureter which exhibits the greatest degree of tone and, having the largest proportion of muscle tissue in its wall, has the greatest propulsive power of the whole organ.

With its three defensive mechanisms assailed, it is perhaps not surprising that dilatation of the upper urinary tract occurs in colonic transplantation and, indeed, appears to be inevitable.

The Ureter in Retention of Urine

As seen on intravenous pyelography, the appearance of the upper urinary tract in chronic retention of urine takes one of the three following forms. Common to all is the presence of residual urine in the bladder.

(1) Normal upper urinary tract.
(2) Dilatation of the lower ureter.
(3) Dilatation of the whole upper urinary tract,
  (*a*) without ureteric reflux.
  (*b*) with ureteric reflux.

Wells (1950) said: "How these changes in the upper urinary tract become established is a matter about which we have insufficient evidence to be dogmatic. So far as our evidence goes, it suggests that the intact ureter does not allow fluid to be forced up and it suggests further that in the prostatic subject, once the process starts, there is a preliminary period in which the lower ureter only is dilated. We think it likely that once established, this progresses relatively quickly to affect the whole ureter, including the renal pelvis with the production of hydronephrosis."

It is suggested that these changes can be explained on the basis of the foregone experimental observations.

The upper urinary tract is affected in retention of urine by the resistance that the intravesical pressure presents to the ejection power of the ureter. This effect will be conditioned more by the tone of the bladder than by the volume of its contents as, in some cases, enormous quantities of the latter are demonstrable with anatomically intact ureters and kidneys. The reverse is true in a common example susceptible to personal observation as when micturition is socially inexpedient. In this instance, the limits of bladder distensibility have been reached, detrusor tone is high and aching in the loins is added to the hypogastric discomfort of a distended bladder. The bladder contents under these circumstances are not great, compared with the residual urine encountered in chronic retention, but nevertheless the kidney is subjected to back pressure as indicated by loin pain.

When obstruction is gradual in onset and progression, the bladder accommodates itself to an increasing volume of its contents by a lowering of tone, as reflected in the notable absence of vesical discomfort, in spite of a large amount of residual urine. Under these circumstances, intravesical pressure will still be within physiological limits, and the upper urinary tract correspondingly of normal function and appearance, as in type 1.

The question arises—what is the normal appearance of the upper urinary tract? As far as the ureter is concerned an acceptable normal ureterogram consists of a ureter outlined in one or more portions by radio-opaque dye. The commonest sites to be so demonstrated are the top, either in continuity with or separated by a small interval from the pelvic shadow, the mid-section and the pre-vesical portion. Having regard to the two modes of urine propulsion, these radiological ureteric spindles could represent either urine proceeding in a "through" peristaltic manner or pool formation with the ureter acting segmentally.

If pyelography is carried out in retention of urine when the bladder pressure is consistently raised then pool formation and segmental activity in the lower portion of the ureter may be anticipated and this feature will show up on the ureterogram as a dilatation of the lower end. This is precisely the picture described as a type 2 change in the upper urinary tract in chronic retention of urine, but is really a response of the ureter within physiological limits.

The next stage will be reached when the physiological limits of intravesical pressure are passed. The ejection power of the lower ureter will now become embarrassed for the first time and back pressure communicated to the remainder of the tract. It has been noted that there is no intermediate stage between dilatation of the lower ureter and that of the whole upper urinary tract. This feature accords with experimental observation that the tone gradient in the ureter diminishes progressively from bottom to top. Thus, when back pressure from the bladder surpasses the limits with which the lower ureter can cope, dilatation of the remainder will occur rapidly as a matter of course, its tone being even less than that which has already been overcome below. No intermediate stage will be seen and the pyelographic appearances are those of type 3.

Defence of the upper urinary tract against back pressure is resident in ureteric tone and the uretero-vesical valve. It has been argued that the early stage of type 3 appearance is reached by an "overstrain" of the ureteric tone mechanism and at this juncture there is no need to involve a failure of the uretero-vesical valve.

However, incompetence of the valve does occur, and can be demonstrated by taking micturition cystograms with the urethra clipped. The normal valve does not allow reflux of bladder contents into the ureter. It owes its competence to the obliquity of the intramural ureter and operates by intravesical pressure compressing the ureter against the backing of muscular bladder wall in a state of tone. Failure of bladder tone, which occurs in advanced stages of chronic retention, amounts to a removal of the resisting wall against which the

ureter is compressed with resultant failure of the valve mechanism. Dilatation of the upper urinary tract will now again increase as it is subjected to the direct effects of intravesical pressure to give the appearance of the last stage of back pressure evolution in chronic retention.

REFERENCES

BEGG, R. C. (1946) *Brit. J. Urol.*, **18,** 176.
ENGELMANN, T. W. (1869) *Pflüg. Arch. ges. Physiol.*, **2,** 243.
FUCHS, F. (1936) *Z. Urol. Chir.*, **37,** 154.
GOULD, D. W., HSIEH, A. C. L., and TINCKLER, L. F. (1955) *J. Physiol.*, **129,** 425, 436, 448.
HANLEY, H. C. (1953) *Brit. J. Urol.*, **25,** 358.
LAPIDES, J. (1948) *J. Urol.*, **59,** 501.
SVENSON, O., MACMAHON, E., JACQUES, W. E., and CAMPBELL, J. S. (1952) *New Engl. J. Med.*, **246,** 41.
TRATTNER, H. R. (1932) *J. Urol.*, **28,** 1.
WELLS, C. A. (1950) *Proc. R. Soc. Med.*, **43,** 43.
WILLIAMS, D. I. (1954) *Ann. R. Coll. Surg. Engl.*, **14,** 107.

Mr. H. G. Hanley said he was not convinced about this question of true peristalsis in the ureter, if by peristalsis was meant "a wave of contraction preceded by a wave of relaxation". Mr. Tinckler had said that if the animal was standing or was tilted feet down the bladder pressure was increased. However, if pyelograms were done on human beings while they were tilted head down there was a marked retention of medium in the renal pelvis. If the ureter was watched under the X-ray image amplifier one could see the opaque medium enter the upper ureter, hesitate and perhaps return to the renal pelvis. If the patient was now turned quickly on to his feet the medium appeared to fall out by gravity, and this made him a little suspicious of the problem of peristalsis. The fluid merely appeared to pour out of one spindle into the next one.

With regard to the action of drugs on the human ureter, animal experiments could be very misleading. The response produced by a drug on an isolated animal ureter could not be repeated in the human being without giving toxic doses. Mr. Hanley had found it impossible to record any electrical or pressure effects on the intact human ureter by giving intravenous morphia or atropine in therapeutic doses, and this applied to most of the other substances which were supposed to affect the ureter.

While Mr. Tinckler's was a magnificent piece of work, he would point out that the organs of the human being behaved very differently from the experimental animal.

Mr. G. F. Murnaghan agreed with Mr. Hanley. During 30 *in vitro* experiments using segments of excised human ureter, chiefly in the upper segment, he had only once seen true peristalsis arise spontaneously with mild distension. In further experiments with the pig ureter he observed that the only characteristic common to both species was that excised segments were completely autonomous. He thought that the various contractions could be explained simply in accordance with the stretch response of the ureteric muscle. He did not think that the nerve supply or particular changes in pressure or posture were responsible for particular contractions or dilatations. When altering the flow in isolated ureters the contractions were irregular, could spread in either direction and could close down the ureter in segments or exhibit conducted contractions.

He was particularly interested in the kinks which could be seen on still or cine pyelograms. Campbell Begg had explained these as being the result of prolapse of cystoids but the pseudo-sphincters defining the cystoids could not be demonstrated anatomically. Electrically there was no difference in the contraction which passed down the unsupported part of the ureter and that which passed through the so-called sphincters where there might be a constriction in the fibrous adventitia. He was hoping to show that the difference in contractions as seen in various segments of the ureter might be due to limitations of the stretch response of the muscle by these fibrous constrictions.

The pressures exhibited in Mr. Tinckler's experiments were unduly high; did the rate of flow into the animal bladder, as indicated, correspond to as high an output as 4½ litres in twenty-four hours?

David M. Davis of Philadelphia had recorded the pressures in the renal pelvis of patients with nephrostomy drainage but apparently normal ureters. He noted that a pressure of 8 cm. of water sufficed to initiate ureteric peristalsis and that the normal pressure varied between 12 and 23 cm. of water.

Mr. D. Innes Williams said that he found when he did some experiments on the rabbit that if the bladder was drained continuously and a diuresis induced the whole ureter was filled: the urine passing through in one continuous stream without much intervention from peri-

stalsis. One occasionally saw a pyelogram in which the whole ureter seemed to be filled; he had seen it in children without any obstruction. One knew that in all mega-ureters, provided there was no infection, the peristaltic function was excellent and he did not quite know how one would measure the tone of the ureter.

Mr. Tinckler, in reply, said that Mr. Innes Williams had noted that at times in the experimental animal urine appeared to pour down the ureter which became an open channel from the renal to the vesical end. He had encountered this himself when diuresis had been induced by injecting about 10 c.c. of fluid intravenously into a rabbit and suddenly raising the renal filtration rate. It was suggested, however, that the circumstances in which the ureter opened up completely to contain an unbroken column of urine from top to bottom were not physiological as under normal condition the animal imbibed water for slaking thirst and not to an extent that would produce a renal excretion rate that would be classified as a diuresis. Mr. Hanley had mentioned the apparent unresponsiveness of the ureter to drugs. This was understandable if peristalsis was regarded as the only attribute of ureteric activity. Perhaps one should look to a more cryptic function of the ureteral musculature as being susceptible to the administration of pharmacological agents such as acetylcholine. The humoral agents of the autonomic nervous system, adrenaline and acetylcholine, could consistently produce tonic contractions in an isolated preparation severed of all connexions but had no effect on peristaltic movement. Other drugs under the same experimental conditions had no action in stimulating tonic contraction. In other words the ureter appeared to be rather particular about the drugs to which it was prepared to respond.

In answer to Mr. Murnaghan's enquiry as to the urinary output in the experimental animals, the figure of 4½ litres in twenty-four hours, which Mr. Murnaghan had deduced from the records Mr. Tinckler had shown was incorrect, as the data disclosed pressure only in absolute units.

Splitting the Kidney for Staghorn Calculus

By Raymond Helsby, F.R.C.S.

Department of Surgery, University of Liverpool

"The patient who has once had staghorn calculi requires urological supervision for life, and the length of that life may be peculiarly dependent upon the judgment of the physician"—so wrote an American urologist recently. Many surgeons have seen patients with large bilateral branched renal calculi who nevertheless may live to a ripe age with minimal symptoms and minimal disturbance of their everyday life. Priestley and Dunn (1949) reviewed a series of 382 patients with branched calculi and found 40% had bilateral disease. A large proportion of these patients were dead ten years after the stones were first detected. A recent spate of papers on the metabolic factors which may lead to renal calcification or calculus formation has made surgeons everywhere keen to find such a cause. Unfortunately, in these cases of extensive calculus disease, careful investigations usually fail to throw any light on the problem. One should be at pains, however, to exclude the presence of a parathyroid tumour, and serum calcium and phosphorus estimations should be carried out in all cases of renal lithiasis.

In the absence of any demonstrable endocrine or metabolic disorder treatment can be of two types—removal of the stone or the institution of a regime to arrest further calculus formation. Such a regime must be directed towards reducing the urinary crystalloid concentration, increasing the protective or stabilizing substances (whatever they may be) and controlling infection. Priestley showed, however, that the survival rate following diagnosis was higher for those treated by operation than for those treated conservatively. Such groups must of necessity be pre-selected to some extent since patients with advanced renal failure would not be accepted for operation.

What operation are we to do? When the extra-renal pelvis is large and the branches of the stone are so formed that it can be extracted through the renal pelvis without extensive trauma, then pyelolithotomy is the operation of choice. Usually, however, an enlarged bulbous end to at least one branch of the calculus makes extraction impossible through the pelvis. If one resorts to fragmentation of the stone some small piece may escape removal and provide a nucleus for further stone formation. Extensive nephro-lithotomy tended to fall into disrepute because of the high incidence of complication—particularly hæmorrhage and sepsis. These complications not infrequently led to a subsequent nephrectomy. Extraction of a large calculus by nephro-lithotomy is a traumatic procedure and small fragments of stone may be left behind. For the large unilateral calculus nephrectomy is often done—but this is surely a bad policy since nearly 40% of these patients develop stones in the opposite kidney. If the kidney be deliberately and completely split in two, and opened out like a book—extraction of a staghorn calculus becomes a relatively simple matter and the

chances of any small fragment being overlooked are greatly diminished. As a further precaution a straight X-ray of the exposed kidney should be taken in the operating theatre.

To minimize the bleeding consequent upon nephrotomy Cullen and Derge (1909) suggested the kidney should be cut open with a silver wire, thus pushing aside the arborizing vessels. Prather (1934) preferred a V-shaped incision through the posterior aspect of the kidney. Jianu (1923) was more concerned with subsequent hæmostasis and recommended multiple U-shaped sutures through the renal substance. There is no general agreement on the length of time during which a clamp may be left on the renal pedicle. Litten (1880) found the extreme limit to be one and a half hours. Marshall and Crane (1923), however, claimed that anæmia for twenty to twenty-five minutes produced definite changes in the character of the urine secreted after blood flow was resumed. Hamilton Stewart (1952) believes the renal vessels should not be clamped for more than twenty minutes. We have left a light clamp on the pedicle for one hour and have seen no untoward sequelæ.

Our technique is to mobilize the kidney and to apply a light rubber-shod intestinal clamp to the pedicle. The kidney is then incised through its lateral border from pole to pole and the incision deepened until the pelvi-calyceal system is entered. The kidney is then "opened" and the stone extracted. The calyces are carefully searched for any small remaining fragments and a check X-ray taken. The generally accepted method of closure after any extensive nephrotomy is by a number of mattress sutures—but this endangers the viability of much functioning renal tissue. We therefore prefer to identify and under-run with fine catgut all the larger vessels which have been divided and then to co-apt the two cut surfaces from within outwards with many delicate sutures. Finally the renal capsule is closed with a running suture. There is no need to insert any fat or muscle tissue as an aid to hæmostasis, but it is important to close the kidney around a nephrostomy tube. This tube is subsequently irrigated to wash out any debris from the renal pelvis.

Professor Wells has performed seven such operations during the past six years and the results have been encouraging. In 2 patients the operation has been done for bilateral staghorn calculi. There have been no deaths and no complications. One kidney which was not functioning pre-operatively has failed to function since the operation. The other intravenous pyelograms are very satisfactory and show only slight deformity of the pelvi-calyceal outline. In 2 patients, despite X-ray control in the operating theatre, small fragments of stone were left in the kidney. So far they have failed to increase in size. At future operations of this type even greater efforts will be made to ensure the removal of all fragments. In 2 other patients small areas of calcification are visible in the post-operative radiographs but no true calculus has formed.

REFERENCES

CULLEN, E. K., and DERGE, H. F. (1909) *Bull. Johns Hopk. Hosp.*, **20**, 350.
JIANU, A. (1923) *Surg. Gynec. Obstet.* **37**, 652.
LITTEN (1880) Quoted by SLAUGHTER, G. L. (1952) *J. Urol.*, **68**, 17.
MARSHALL, E., and CRANE, M. (1923) *Amer. J. Physiol.*, **64**, 387.
PRATHER, G. C. (1934) *J. Urol.*, **32**, 578.
PRIESTLEY, J. T., and DUNN, J. H. (1949) *J. Urol.*, **61**, 194.
STEWART, H. (1952) *Ann. R. Coll. Surg. Engl.*, **11**, 32.

Mr. H. F. Lunn, after his experience in the Middle East in the treatment of calculous anuria, supported Mr. Helsby in his technique. He preferred to approach a staghorn calculus via separate incisions through those areas of the kidney substance which were thinned out over the branched ends of the underlying calculus. Though the stone had to be removed piecemeal, bleeding was easily controlled and function was quickly restored. Such an approach enabled the operator to explore each of the calyces and to remove most of the fragments which as Mr. Helsby had said evaded X-ray detection in the theatre during the kidney-splitting operation.

[*March* 22, 1956]

THE following cases and specimens were shown:

Nephrectomy Showing Condition of Pelviureteric Anastomosis Four Years after Anderson Hynes Pyeloplasty.—Mr. B. H. PAGE.

(1) **Papilloma of Renal Pelvis.** (2) **Carcinoma of Renal Pelvis.**—Mr. J. GABE.

Renal Tumour with Misleading Features.—Mr. C. C. WIGGISHOFF (for Mr. A. R. C. HIGHAM).

Anuria of 17 Days' Duration Associated with Fits.—Dr. F. M. PARSONS.

Vesical Exstrophy with Malignant Change.—Mr. J. O. HARRISON.

Phæochromocytoma of the Bladder.—Dr. R. C. B. PUGH.

Carcinoma of Prostatic Urethra.—Mr. ASHTON MILLER.

Interstitial Celled Tumour of Testicle Causing Premature Puberty.—Mr. D. P. VAN MEURS.

Seminoma of Testis, Weighing Over 8½ lb.—Mr. J. GABE.